Cortical representation of motor imagery, observation, and performance in chronic complete spinal cord injury

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PREFACE

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I wish to tank my parents Willi and Rahel Hotz for their unconditional love and support.

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I dedicate this thesis to my dear girls, Anna Sofie and Lynn Elise who always remind me of what is truly important in life.

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1. ABSTRACT

English abstract

Patients with spinal cord injury (SCI) provide a human model in which the effects of de-afferentation and de-efferentation on brain activation can be studied. The present thesis addressed the cortical representation of motor imagery, movement attempt and observation of foot movements in chronic complete paraplegics. Brain functions of both healthy subjects and SCI patients were investigated with behavioral and neuroimaging methodologies. The three studies, part of the present thesis, investigated the following questions, each addressing different aspects of movement generation and control. (1) What is the influence of SCI on motor imagery and what does it tell about motor imagery in healthy subjects? (2) Can SCI patients differentiate between attempted and imagined movements and are motor commands still present? (3) Can movement observation in SCI patients activate the observation/execution matching system as in healthy subjects and thus be a reliable proof for the existence of motor representation? The results of the first study revealed that motor imagery in SCI patients activated in parallel both the motor execution and motor imagery networks of healthy subjects. The findings provided new insights on the neuroanatomy of motor imagery and the possible role of kinesthetic feedback in the suppression of cortical motor output required during covert movements. The second study showed the retained integrity of movement attempt and motor imagery networks in SCI patients and suggests that these patients can still dispose of the full motor program for foot movements. Therefore attempted and imagined foot movements should be integrated in rehabilitative strategies. The results of the third study confirm the findings of the first two studies. Foot movement observation activates the motor system as postulated in the theory for the execution/observation system. These results are discussed in the context of present theories of motor control and of plasticity after sensory deprivation. The findings are highly relevant, clinically as well as for basic neurosciences, as they provide converging evidence for remnant motor representation in these patients. The preserved motor capability, responding to intent and observation, is an important issue in future rehabilitative strategy.

Deutscher Abstract

Patienten mit einer kompletten Rückenmarkverletzung stellen ein menschliches Modell dar, in dem Effekte der Deafferenzierung und Deefferenzierung auf das sensomotorische System studiert werden können. Die vorliegende Dissertation untersuchte die kortikale Repräsentation von Fussbewegungen während Bewegungsvorstellung, Ausführung und Beobachtung bei chronisch kompletten Paraplegikern. Die Hirnfunktionen von gesunden Versuchspersonen und paraplegischen Patienten wurden mit Verhaltenstests und bildgebenenden Verfahren untersucht. Die vorgestellten drei Studien untersuchten unterschiedliche Aspekte der Bewegungsausführung und deren Kontrolle mit den folgenden Fragestellungen: (1) Wie beeinflusst eine Rückenmarkverletzung mentale Bewegungen? (2) Können Paraplegiker zwischen ausgeführten und mentalen Bewegungen unterscheiden? (3) Kann die Beobachtung von Bewegungen in Paraplegikern das gemeinsame System für Ausführung und Beobachtung von Bewegungen aktivieren? Die Resultate von Studie 1 zeigten, dass mentale Bewegungen bei Paraplegikern gleichzeitig die Netzwerke für ausgeführte und für mentale Bewegungen aktivierten. Dieser Befund führte zu neuen Einsichten über die Neuroanatomie mentaler Bewegungen und der möglichen Rolle des kinästhetischen Feedbacks, das zur Unterdrückung der Bewegungsausführung nötig ist. Studie 2 zeigte die erhaltene Fähigkeit eigenständiger motorischer Netzwerke für ausgeführte und mentale Bewegungen bei Paraplegikern. Im Weiteren scheinen diese Patienten über das volle motorische Programm für Fussbewegungen zu verfügen. Daraus folgt, dass sowohl ausgeführte als auch mentale Bewegungen in Rehabilitationsprogrammen integriert werden sollten. Die Resultate von Studie 3 bestätigen die Befunde der beiden ersten Untersuchungen. Wie in der Theorie postuliert, aktivierte die Beobachtung von Bewegungen die gleichen motorischen Hirnareale, die bei Bewegungen aktiv wurden. Die Ergebnisse der Studien werden im Kontext gegenwärtiger Theorien über motorische Kontrollmechanismen und Plastizität nach sensorischer Deprivation diskutiert. Die Befunde über die erhaltene motorische Repräsentation bei paraplegischen Patienten sind äusserst relevant, sowohl für die Klinik, als auch für die Grundlagenforschung in den Neurowissenschaften.

2. GENERAL OVERVIEW

Over the past years significant knowledge has been gained on the organization and reorganization of the motor cortical and subcortical regions. With the advent of modern neuroimaging (i.e., positron emission tomography (PET), functional magnetic resonance imaging, fMRI) extensive research on the functional specialization of the various motor areas has been undertaken in non-human primates and in humans. The non-invasive neuroimaging tools additionally facilitated extension of the investigations on body representations in several patient groups. This thesis deals with plastic changes in the sensorimotor system after complete spinal cord injury (SCI). A spinal cord injury is a lesion of the spinal cord that results in a loss of functions, such as mobility or sensory perception. Frequent causes of damage are trauma (car or sport accident, falls, etc.) or disease (tumor, spina bifida, etc.). Patients with SCI provide a human model in which the effects of deafferentation and deefferentation on sensorimotor maps can be studied. The thesis comprises three functional imaging studies investigating activation patterns for imagined, real and observed movements in healthy controls and their changes in SCI patients. It further discusses the general implications of the findings for the understanding of sensorimotor control and in particular for new rehabilitation strategies. In the following, a brief theoretical introduction on motor behavior and its central control as well as on simulated and observed actions is presented as the basis for discussing the results of the three studies.

2.1. The motion in one's mind

An action is the means of interaction or reaction of a person with the external world. The human motor system can generate accurate movements under widely varying conditions. Therefore actions can be described as the final expression of several information preprocessing stages: intention, programming, preparation, and execution. These motor acts are centrally represented and, like other representations, are stored, modified and may be retrieved through specific cognitive processing. It is generally thought that cognitive processes, resulting in "overt" or executed motor behavior and "covert" or simulated behavior are intimately related. Jeannerod (2001) defined covert actions as real actions, except for the fact that they are not executed. Imagination and observation of movements are both covert behavior triggering the stored motor programs used to execute that action (Jeannerod, 1994).

2.1.1. Motor control

Over recent years the concept of an internal model, a system that mimics the behavior of a natural process, has emerged as an important theoretical concept in motor control (Kawato *et al.,* 1987). Forward models map the relationship between motor commands and the resultant changes in the state of the motor system, which are monitored by reafferent sensory inflow. The sensory input provides information about the state of the world, as well as information about the state of our own body. In addition to these sensory inputs, the central nervous system (CNS) can monitor its own activity. For example a copy of the motor output can be used to provide information about the ongoing movement. This signal is known as the efference copy or corollary discharge to reflect that it is a copy of the cortical signal flowing out of the CNS to the muscles (Von Holst and Mittelstaedt, 1950, the concept of efference copy was established by the work of Von Holst and Sperry in the 1950s). Hence, a forward model estimates the next (sensory) state of the motor system based upon information on its current state, its dynamics, and the current motor commands issued.

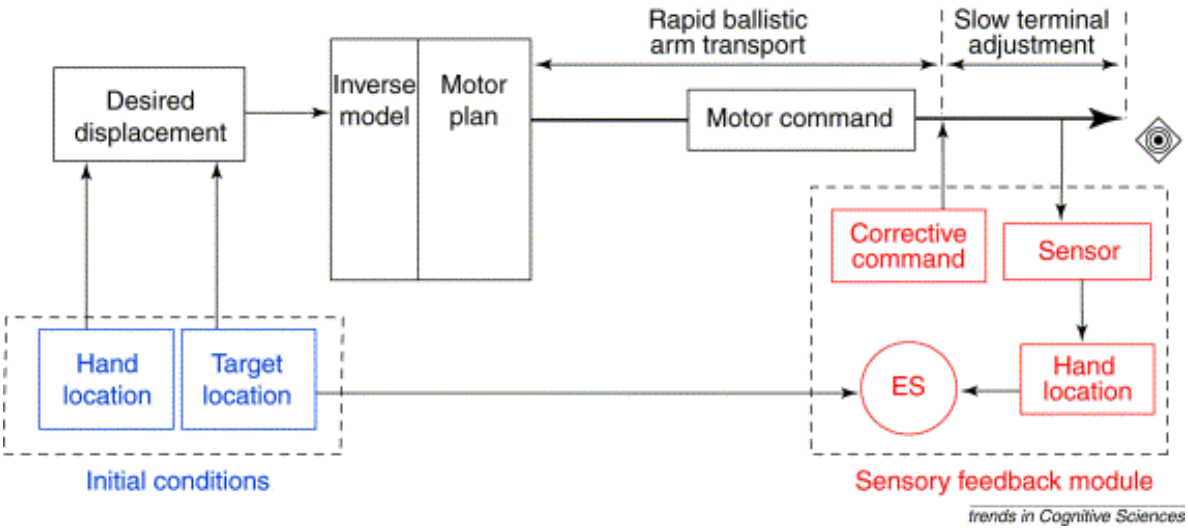


Figure 1. The classical dual model of movement control. The required arm displacement is estimated based on the respective locations of the hand and target. This displacement is then converted into a motor plan through an inverse model. The main part of the movement unfolds under the rigid control of this plan (ballistic arm transport). Sensory feedback loops become active at the very end of the movement, when velocity is low. The current location of the hand is then compared to the target position. In case of a discrepancy, an error signal (ES) is issued and a series of corrective sub-movements is generated. The movement stops when the hand reaches the target (circle in diamond) (from Desmurget and Grafton, 2000)

The accuracy of each forward model prediction to the actual state allowed the current sensorimotor context to be estimated. Only the right model for a given context would accurately predict movement outcome. So if your movement to grab an apple matches your prediction, you trust that the context (apple on the table) was correct and that you have not mistakenly grabbed the table instead. Forward models are not fixed entities but must be learned and updated through experience. They can be trained and updated using prediction errors, by comparing the predicted and actual outcome of a motor command (Wolpert and Miall, 1996; Wolpert and Ghahramani, 2000).

2.1.1.1. The body schema

The integration of the efference copy and the reafferent sensory inflow has been hypothesized to produce an on-line, real-time representation of the body position in space, also called “body schema”. An important feature of the body schema is that it usually does not enter into awareness. (Coslett, 1998; Coslett *et al.*, 2002). This construct has recently been described by Schwoebel and Coslett (2005, p.543).

"Consistent with classic accounts suggesting multiple representations of the human body (e.g., Pick, 1922; Head and Holmes, 1911–1912), recent evidence suggests that there are at least three distinct types of body representations. The first, termed the body schema, is a dynamic representation of the relative positions of body parts derived from multiple sensory and motor inputs (e.g. proprioceptive, vestibular, tactile, visual, efference copy) that interacts with motor systems in the genesis of actions (e.g. Schwoebel et al., 2002). The second representation, termed the body structural description, is a topological map of locations derived primarily from visual input that defines body part boundaries and proximity relationships (e.g. Buxbaum and Coslett, 2001; Sirigu et al., 1991). The third human body representation, which has been called the body image or body semantics, is a lexical–semantic representation of the body including body part names, functions, and relations with artifacts (e.g. Coslett et al., 2002). Several converging lines of evidence support the psychological validity of and distinctions between these three types of human body representations".

In the context of this section, only the body schema will be discussed. The knowledge of the anatomical areas involved in the maintenance of the body schema largely comes from the clinical literature (for a classical treatment of the issue see Critchley, 1953). Patients suffering from disturbances of body schema representation often have infarcts in the parietal lobes, particularly in its inferior lobe. The superior parietal lobe has a key role in sensorimotor integration, by actively maintaining an internal representation of one's body. Alternatively, it is possible that this representation may be separate from those used for directing attention on holding a body schema. (Wolpert *et al.,* 1998). Infarcts in the right parietal lobe may typically result in the unawareness of body parts and sensations, as for instance in the syndromes of neglect (Coslett, 1998) and anosognosia (Berti *et al.,* 2005), while lesions in the left parietal lobe may produce difficulties in the identification of body parts as is typically the case in the Gerstmann syndrome (Gerstmann, 1930)

2.1.1.2. Functional localization of the forward model

It is highly likely that the parietal areas and the cerebellum work as functional loops for estimating the current status of the motor system throughout movement execution. Sensory signals from different modalities (e.g. visual, proprioceptive, auditory and vestibular), as well as efferent copy signals from motor regions, are integrated in the PPC (Andersen *et al.*, 1997). This is concurring with the idea that sensorimotor integration is a crucial feature of forward models. The cerebellum receives a large input from fibers descending from the motor cortex, via the pons and it is thought that these represent the efferent copy of outgoing motor commands. The cerebellum also receives important proprioceptive information directly from the ascending dorsal spinocerebellar tracts which provide an update of the state of the motor apparatus. Miall and Wolpert (1996) suggested that the cerebellum's role in these diverse tasks is to provide the forward model estimates and predictions of the state of the motor system. Finally, pervious studies have shown that the cerebellar cortex can acquire internal models through motor learning. (Imamizu *et al.*, 2000). The parietal cortex receives input from the cerebellum via the thalamus and there are connections in the opposite direction via the pons (Glickstein, 2000). Parallel processing allows to predict the sensory consequences of movements and to monitor and to make corrections to on-going movements. (Blakemore and Sirigu, 2003).

2.1.2. Imagination of movements

Behavioral investigations showed that imagined actions retain the same temporal characteristics, have similar anatomical limitation and induce comparable physiological activations as the execution of the same motor task (Decetey & Jeannerod, 1995; Jeannerod & Decety, 1995 Decety *et al.,* 1989). In line with this psychological and physiological evidence are a number of studies reporting functional nervous circuits shared by movement execution and motor imagery (for a summary see Jackson *et al.,* 2001; Lafleur *et al.,* 2002). Numerous functional imaging studies have addressed the question of the neuroanatomical substrate of motor imagery with a large variety of behavioral tasks, a wide range in task complexity, and several methodological differences. As emphasized by Jeannerod (1995) two kinds of mental representations of the self in action can be generated: internal or kinesthetic images, corresponding to the representation of the action from within (first person process) and external or visual images involving a visuospatial representation of an action performed by somebody else (third person process). Subjects need specific instructions and ability to have the actual feeling of performing internally the action and avoid visualization (Solodkin *et al.,* 2004).

Early cerebral blood flow experiments reported during imagined hand movements mainly SMA activation, but no primary motor cortical (M1) involvement, (Roland *et al.,* 1980). Subsequent work performed with fMRI and PET demonstrated more detailed functional specificity within brain regions involved in simulation. An early fMRI study demonstrated that pixels activated during contraction of a group of muscles are also activated during imagery of a movement involving the same muscles (Roth *et al.,* 1996). Additional studies of imagined movement demonstrated involvement of PMv, PPC, the superior temporal sulcus (STS), cerebellum and, rarely, M1 (Binkofski *et al.,* 2000; Decety, 1996; Grafton *et al.,* 1996; Nishitani and Hari, 2000; Stephan *et al.,* 1995, Lafleur *et al.,* 2002). Primary motor cortex activation reported during motor imagery amounts about 30% of the level observed during execution. It may not be found in all subjects (Porro, 1996; Gerardin *et al.,* 2000).

The degree of coincidence between the neural structures involved in motor imagery and motor generation remains controversial. Although imagination of hand movements involves many cortical areas also subserving motor execution (Lotze *et al.,* 1999; Porro *et al.,* 1996; Stephan *et al.,* 1995) the systems responsible for either function do not overlap completely

(Gerardin *et al.,* 2000, Hanekawa *et al.,* 2003). Porro *et al.* (1996) showed that areas activated during both motor performance and motor imagery represent a large fraction of the whole population of areas activated during motor performance (see also Lotze *et al.*, 1999).

2.1.3 The "mirror-neuron" system

There is a large body of evidence that, in monkeys and humans, several brain regions are activated both during action generation and during the observation of a similar action (Decetey *et al.,* 1997; Grafton *et al.,* 1996; Hari *et al.,* 1998; Rizzolatti *et al.,* 1996). The discovery of mirror neurons has lead to many different speculations about their functional role.

2.1.3.1. Mirror neurons in monkeys

Mirror neurons were first identified and characterized in the monkey brain by Rizzolatti and his co-workers (di Pellegrino *et al.,* 1992; Gallese *et al.,* 1996; Rizzolatti *et al.,* 1996): A class of visuomotor neurons in the area F5 of the monkey ventral premotor cortex was shown to be activated both during execution and observation of hand actions. These neurons are called mirror neurons. The observed actions that are capable of inducing a discharge of the mirror neurons include placing or taking objects from a table, grasping food and manipulating objects (Gallese *et al.,* 1996; Rizzolatti *et al.,* 1996). There is some congruence between the effective observed and executed action (di Pellegrino *et al.,* 1992). Some of the mirror neurons are activated during observation and execution of only one type of action, whereas others show broader congruence and their activation is merely defined by the goal of the action. The monkey mirror neurons do not discharge when the same action is made with a tool or when only an object or an agent is presented.

Mirror-neuron-type behavior has also been found in other parts of the monkey brain. A set of neurons in the inferior parietal lobule, area PF, discharged during both execution and observation of goal-directed hand actions (Fogassi *et al.,* 1998; Gallese *et al.,* 2002). Furthermore, Perrett and his co-workers (Perrett *et al.,* 1989) have described neurons in the anterior part of the monkey superior temporal sulcus (STS) that discharge during observation of biological motion and some of them specifically during observation of goal-directed hand actions. However, these neurons do not seem to exhibit clear motor properties since only a

cortical area that is active during both execution and observation of an action can be considered to have mirror properties (Rizzolatti *et al*., 2001).

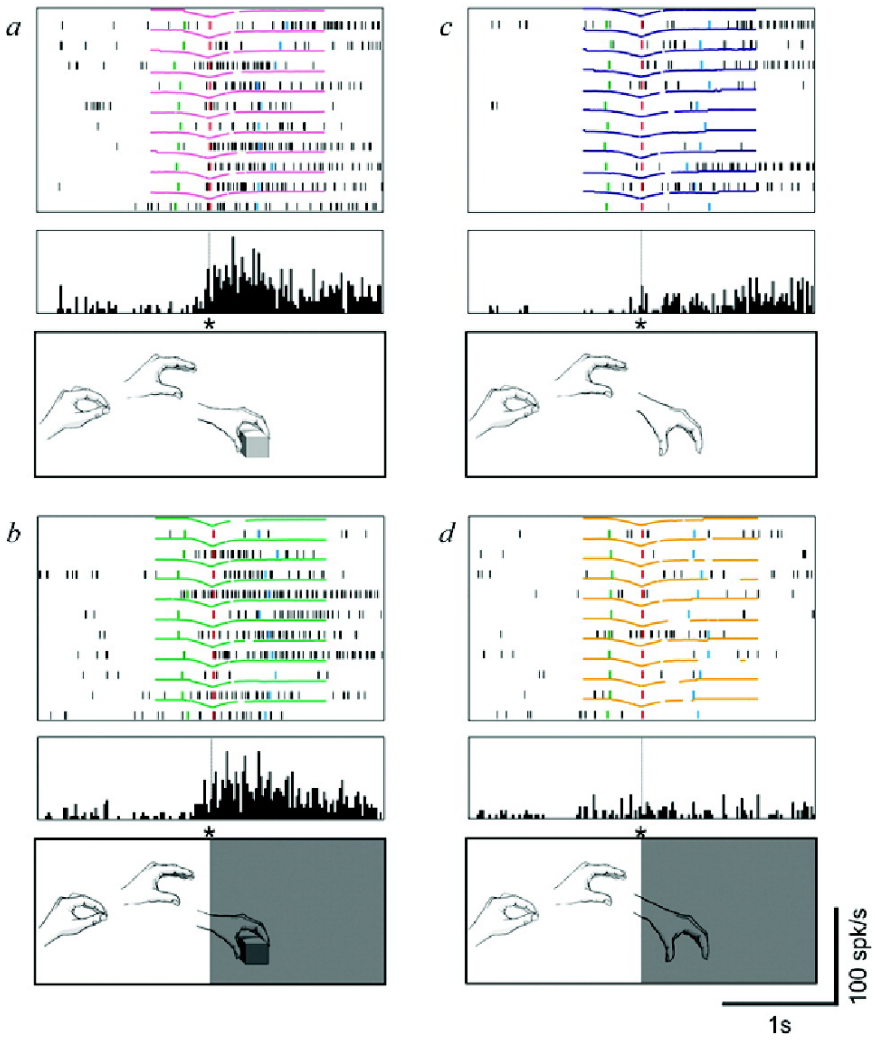


Figure 2. Mirror neuron responses to action observation in full vision (A and C) and in hidden condition (B and D). The lower part of each panel illustrates schematically the experimenter's action as observed from the monkey's vantage point. The asterisk indicates the location of a stationary marker attached to the frame. In hidden conditions the experimenter's hand started to disappear from the monkey's vision when crossing this marker. In each panel above the illustration of the experimenter's hand, raster displays and histograms of ten consecutive trials recorded are shown. Above each raster, the colored line represents the kinematics of the experimenter's hand movements expressed as the distance between the hand of the experimenter and the stationary marker over time. Rasters and histograms are aligned with the moment when the experimenter's hand was closest to the marker. Green vertical line: movement onset; red vertical line: marker crossing; blue vertical line: contact with the object. Histograms bin width = 20 ms. the ordinate is in spike/s. (from Rizzolatti and Craighero, 2004).

The knowledge of the extent of the monkey mirror-neuron system (MNS) is rather limited, since the data is merely based on single-neuron recordings that do not allow simultaneous recordings from different parts of the brain.

2.1.3.2. The mirror-neuron system in humans

After the discovery of the mirror neurons in monkeys, the next natural question was whether a similar action observation/execution matching system would exist in the human brain. Motor evoked potentials (MEPs) elicited by a transcranial magnetic stimulation (TMS) and recorded from hand muscles, were significantly increased during observation of movements involving the same muscles (Fadiga *et al.,* 1995). However, these data did not specify the anatomical level of the effect. During recent years several functional brain imaging studies have provided evidence about existence, circuitry and function of the human mirror-neuron system. According to the functional imaging data the human MNS appears to be more widespread than in monkeys. The observation of an action recruits a consistent network of cortical regions, including ventral premotor cortex (PMv) and the parietal lobes (Fadiga *et al.,* 2005). These areas form the core region of the mirror system, but some additional regions as primary sensorimotor cortex and the cerebellum have also been reported (Avikainen *et al., 2002,*, Hari *et al., 1998,* Grafton *et al.,* 1996). In addition, the STS region which showed activation during both observation and imitation of hand and mouth action is closely connected to the MNS. However, since STS has not been shown to be activated during just execution of an action, it cannot at present be regarded as one of the actual mirror-neuron areas. In some brain regions a highly specific overlap between action observation and action execution seems to be present. The network underlying human action observation revealed with fMRI has the greatest activity when an individual observes an action that he or she is able to perform, when compared to observation of physically impossible movements (Costantini *et al.,* 2005), movements made by a conspecific versus a non-conspecific (here a monkey or a dog, Buccino *et al.,* 2004), or familiar dance movements (Calvo-Merino *et al.,* 2005). Behavioral studies have demonstrated interactions between action perception and execution (Brass *et al.,* 2000; Hamilton *et al.,* 2004) and provided additional evidence to the idea of overlapping neural processes for action observation and execution.

This matching observation/execution system offers a possible explanation of how we understand the actions of others by a direct mapping of the visual representation of the observed action into our motor representation of the same action (Rizzolatti *et al.,* 2000). This interpretation is also compatible with the simulation theory, which assumes that when one observes the actions of others, one covertly simulates the same action (Jeannerod, 1994).

It has also been suggested that the mirror neurons generate an internal representation of the action that can be used for different functions, including recognition and understanding motor events, motor learning, and imitation (Jeannerod 1994; Gallese *et al.,* 1996; Rizzolatti *et al.,* 1996). At present, this concept and its consequences for behavior are considered on the cognitive level as equivalent to "mind-reading," the ability for normal people to understand and predict the behavior of their conspecifics.

Finally, Blakemore and Frith (2005) have suggested that the mirror neurons seem to be a part of a much wider system which has at least three levels. At the lowest level an automatic contagion of the observed movements is occurring, as long as these are made by biological entities. The next level is the mirroring of specific goal-directed actions. Even higher levels, on which intentions are imitated when one knows what the intentions, are is likely. Still open is the question of how the representation of an observed movement (in egocentric coordinates) gets converted into the representation of a goal-directed action (in object centered coordinates).

2.2. The sensorimotor system after spinal cord injury

Central nervous system injuries are particularly traumatic owing to the limited capabilities of the CNS for repair. As a consequence, large motor and sensory deficits persist long after brain or spinal cord trauma, usually throughout life. In cases of spinal trauma, the disruption of nerve fiber bundles that convey ascending sensory and descending motor information is especially devastating, as it results in pronounced and persistent sensorimotor dysfunctions for all body parts below the lesion site (Raineteau and Schwab, 2001). Spinal cord injuries can be typically classified as complete and incomplete. The neurological and functional classification is assessed clinically with the impairment scale of the American Spinal Injury Association (ASIA, Maynard *et al.,* 1997). Electrophysiologically examinations by motor evoked potentials (MEP), transcranial magnetic stimulation (TMS) and somatosensory evoked potentials (SSEP) are applied to verify the clinical data.

The mechanisms of sensorimotor system reorganization after lesion are incompletely understood. The possible mechanisms in response to alteration of the usual sensorimotor input-output patterns involve sprouting, i.e. an increased number of active intracortical synapses onto preserved corticofugal neurons, and/or unmasking of previously inactive

intracortical or corticospinal connections. Pathological changes following SCI trauma include both anterograde axonal degeneration and retrograde cell death (Kalb and Strittmatter, 2000). However, manual measurement and automated voxel-based morphometric analysis did not reveal any significant differences in grey or white matter volume within an M1 region (precentral hand knob) of interest. These data suggest that no gross anatomical changes within M1 are occurring following cervical SCI (Crawley *et al.*, 2004).

2.2.1. Activation changes and somatotopy in upper-limb movements in SCI patients

Patients with SCI provide a human model in which the effects of de-afferentation and de-efferentation on sensorimotor maps can be studied. During the last years several groups have addressed the organization of the cortical hand representation after spinal cord injury (SCI). They were investigating the effects of a distant spinal lesion onto cortical plasticity of a limb that had never been impaired. Some studies looked at activation changes by assessing with transcranial magnetic stimulation (TMS) responses in the muscles that are closely adjacent to the level of lesion. These neurophysiological experiments revealed that motor evoked potentials to TMS resulted in an enlargement of cortical maps of targeting muscles proximal to the injury in tetraplegics (Topka *et al.*, 1991) and paraplegics (Cohen *et al.*, 1991). This plastic changes can be observed as early as 6 to 17 days after injury for the biceps muscle in patients with complete lesions of the cervical spinal cord (Streletz *et al.*, 1995). With functional magnetic resonance imaging (fMRI), Curt *et al.* (2002a) reported for paraplegics compared with a statistical representative control group stronger activation in primary sensorimotor, premotor, and parietal cortex and in the cerebellum. This effect was most frequent and prominent for finger and hand movements in comparison with wrist and elbow movements. Similar cortical areas with larger activations have been reported in other investigations with fMRI in paraplegics (Sabbah *et al.*, 2002; Turner *et al.*, 2003) or with positron emission tomography (PET) in quadriplegics (Bruehlmeier *et al.*, 1998) and in a mixed group of para- and quadriplegics (Curt *et al.*, 2002b). The extensive activation changes in primary and non-primary motor areas and in subcortical regions demonstrate that

even distant neuronal damage has impact upon the activation of the whole sensorimotor system.

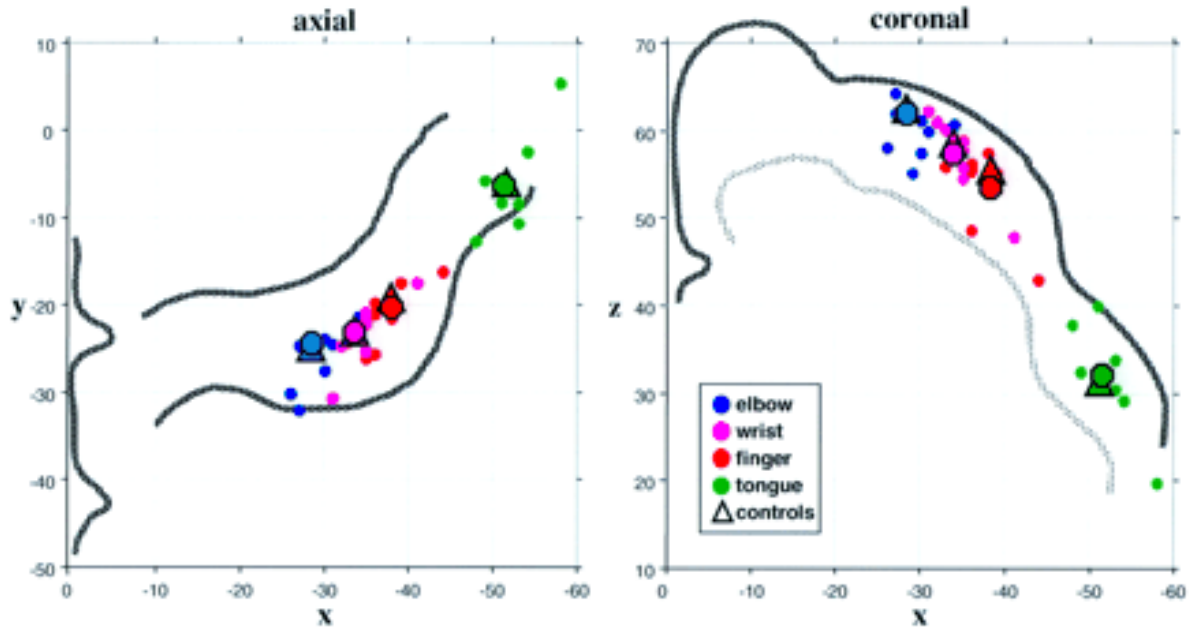


Figure 3. Two-dimensional scatter plots of the individual COGs for the nine SCI patients in the contra lateral M1 (small dots). The mean COGs of the patients are indicated by larger, encircled dots and the mean COGs of the controls by triangles. Note the intact somatotopical gradient of the within-arm and the left hemispheric tongue representations on both axial and coronal planes (with almost identical mean coordinates for all movements in the SCI patients and in the controls). Note also the absence of shift towards the deafferented and deefferented M1 foot area. Left: axial plane with approximate contour of the precentral gyrus. Right: coronal plane with cortical surface and limit to the white matter. x, y, z: coordinates corresponding to Talairach space (Collins et al., 1994).

Beside enhanced cortical activation different ways of reorganization has been described. A posterior shift of cortical activation has been reported using electroencephalography (EEG, Green *et al.*, 1998) and fMRI (Turner *et al.*, 2003). A PET study in contrast reported that the cortical hand activation was invading the disconnected foot area (Bruehlmeier *et al.*, 1998). A similar finding was shown in an fMRI study where the arm/shoulder area was overrunning the proximal “leg area” without displacement of the hand representation (Perani, 2001). Finally Lotze *et al. (*1998) using fMRI found reorganization in the primary motor cortex (M1) as a cranial displacement for elbow but not for thumb movements.

In contrast to these investigations, voluntary activation of sensorimotor representations occurred with only minimal reorganization of the gross somatotopy in subjects within five years of SCI (Shoham *et al.*, 2001). Based on single subject analysis, a similar finding was reported by Curt *et al.* (2002a) who showed that the gross somatotopical organization in M1 for the upper limb was preserved similar to the one obtained in the control population, without shift into the disconnected lower limb representation. These results indicate that in

paraplegic patients the representation of the non-impaired upper limb muscles is functionally modified, though without any topographical reorganization in M1. A similar result has been found in a recent complementary study when SCI patients performed mental rehearsal and movement observation of hand movements (Hotz-Boendermaker, in prep.).

2.2.2. Foot movements in SCI patients

Since M1 has been active during motor imagery in a previous fMRI study (Porro *et al.*, 1996) it seemed feasible to investigate the M1 location and possible alterations in SCI patients with movement simulation (Lotze *et al.*, 1998). Imagined foot movements were measured with fMRI and compared with results obtained in healthy controls. Simulated foot movements showed no significant activation in the precentral gyrus in all patients. However, the patients already mentioned before scanning that they were not able to imaging movements of their deafferented feet. In a similar task the only activation increase reported by Cramer *et al.* (2005) was detected in a specific part of the superior temporal gyrus (area MT), important region for the perception of biological motions. In their study, videos showing a foot hovering over an object to crush were presented with the instruction to imagine movement completion, which may have induced visual motor imagery instead of kinesthetic imagination (Solodkin *et al.*, 2004). Sabbah *et al.* (2002) on the other hand reported inconstant activation in M1 and some non-primary motor areas during self-paced mental simulation of bilateral toe movements. On the basis of qualitative comparisons these authors concluded that the M1 activation patterns in the SCI patients only partly differed from those during execution in the control group. Only a few studies have assessed brain activity in SCI patients during attempted movements of the foot. Activation of the primary motor cortex during foot movements in SCI patients has been reported with event-related potentials (Halder *et al.*, 2006; Lacourse *et al.*, 1999) and, using fMRI, in paraplegics (Sabbah *et al.*, 2002), in tetraplegics (Shoham *et al.*, 2001), and in a mixed group of para- and tetraplegics (Cramer *et al.*, 2005). Sabbah *et al.* (2002) in paraplegics and Cramer *et al.* (2005) in both paraplegics and tetraplegics have compared cortical activation patterns involved in motor control during movement attempt and a control group. Relative to healthy controls, activation was reduced in almost all regions.

2.3. Aims of the studies

The aim of this thesis was to investigate imagination, execution and observation of foot movements by using fMRI in healthy controls and chronic complete paraplegics, and to examine plastic changes due to a complete deefferentation and deafferentation.

The specific goals of Studies1-3 were:

1. To investigate brain activation patterns in SCI patients during motor imagery and compare the findings with data from a control group.
2. To find out whether complete paraplegics can differentiate attempted from imagined foot movements, applying a behaviorally well-controlled paradigm and investigating brain activation patterns.
3. To establish the existence of the human action observation/execution matching system for foot movement and to demonstrate its existence in a patient group with complete deafferentiation and deefferentiation.

The following working hypotheses have been be tested for Studies 1-3:

1. Hypothesis

Imagined foot movements activate the stored motor programs in complete paraplegics. In addition, the different activation networks of the control and the patient group might reveal the central source of movement suppression during motor imagery, and/or the plastic changes induced by the paraplegic condition.

2. Hypothesis

Study 1 revealed a parallel activation of the execution and imagination networks in SCI patients when they were asked to imagine a foot movement. The isolated performance of either attempted or imagined foot movements in SCI patients should therefore reveal different activation patterns. However, when compared with activation found in a control group similar motor networks should be engaged.

3. Hypothesis

Results in Study 2 indicate that complete paraplegics are able to activate different motor circuits for attempted and imagined foot movements although task performance can not be estimated from outside. Based on its definition, the mirror-neuron system should provide the means to externally trigger an internal representation of an action. We therefore expect a similar activated network for observed foot movements in SCI patients and controls and investigated this in Study 3.

Imagined and attempted foot movements in SCI patients have previously been investigated. However the results of the studies described in the review (see section 2.2.) are difficult to compare due to methodological limitations. In the following there are several reasons listed why Study 1 and 2 extend the previous findings and why Study 3 was designed.

1. *Group homogeneity*. Earlier studies investigated in-homogenous and often very small patient populations. They often consisted of mixed paraplegic and tetraplegic patients groups, and/or subjects were included with a rather inconsistent time interval after injury (i.e. from a few months to many years). In addition, most studies were not referring to the completeness of the lesion, often not tested with common neurophysiological methods. The three studies presented in this thesis consisted of patient groups with at least 8 complete paraplegics. Completeness of lesion was in all participants examined with standardized neurological and physiological methods at several times after injury. Finally, in Study 2 and 3 they were at least 2 years after injury, a time interval that is generally considers a chronic state.
2. *Regions of interest.* Previous studies focused on selected cortical areas as the primary and secondary sensorimotor cortex. The present studies addressed the high behavioral variability in the performance of motor tasks and considered cortical and subcortical motor regions of the whole brain.
3. *Single subject analysis.* Former studies did present results from group activation providing a general overview on activated brain areas. However, when looking for plastic changes in the sensorimotor system of patients, the analysis of data in single subjects is an important issue yielding important additional insights for the explanation of the data.

4. *Behavioral assessments*.

   Task control. Foot movement tasks in complete paraplegics are not controllable from outside. Therefore in Study 2 and 3 attempted and imagined movements were previously assessed and trained with behavioral tests in order to have an additional means of measurement.

   Subjective experience of movements. Earlier studies investigated motor performance in SCI patients either with behavior tasks or used neuroimaging methods without combining them. In addition, the subjective experience of movements was not investigated. However, data on the experienced vividness of movements as assessed by telephone in Study 1 can add important additional information if correlated with fMRI data. In Study 2 and 3 a structured interview was developed for evaluating static phenomena, paresthesias and movement sensations. Data from the interviews and fMRI experiments were statistically analyzed. In fact, correlations between neuroimaging data and clinical data can further explain the impact of injury on movement performance and plasticity in patients.

5. *Movement observation.* Observation of movement has not been investigated in SCI patients so far. Based on the parallel activation of observed and executed actions in the motor system, observation could become an additional tool to assess movement representation in plegic patients.

2.4. Research studies

2.4.1. FMRI study on motor imagery of foot movement in SCI patients (Study 1)

The first study presented here (Study 1, see 3.1.) was designed to explore the simulation of foot movements in complete paraplegics and its comparison with the data of a control group.

H Alkadhi, P Brugger, S Hotz-Boendermaker, GR Crelier, A Curt, MC Hepp-Reymond and SS Kollias (2005). **What disconnection tells about motor imagery. Evidence from paraplegic patients.** *Cerebral Cortex, 15, 131-40.*

The task in Study 1 was a self-paced dorsal and plantar flexion of the right foot, first imagined in both groups, followed by execution of the same movement in the control group. In addition the SCI patients were interviewed by telephone about their vividness to imagine foot movements. The result of Study1 demonstrates that stronger activation was detected in primary and all non-primary motor cortical areas and in subcortical regions in SCI patients when compared to the healthy population. In fact, motor imagery in SCI patients activated in parallel both the motor execution and motor imagery networks of healthy subjects. This result provides strong evidence that in a patient group with complete deafferentiation and deefferentiation, the primary motor cortex still engages the template of movements as suggested previously for covert movements by Jeannerod (1995).

Author contributions. HA, MCHR, SSK and GRC conceived and designed the experiments. AC recruited the patients and contributed materials. HA, SHB, GRC and SSK performed the experiments and analyzed the data. PB conducted the telephone interview. SHB performed the statistic analysis.

2.4.2. FMRI study on motor control of foot movements in SCI patients (Study 2)

The first study provided strong evidence that patients with complete deafferentiation and deefferentiation are still engaging the central machinery of movements. This earlier experiment however, made no clear distinction between motor imagery and movement attempt, an issue not systematically investigated in SCI patients so far. In Study 2 (see 3.2.) the remaining degree of motor control was assessed in complete paraplegics, more precisely their ability to differentiate between imagined and attempted foot movements. An important issue here is the control of limb movement since knowing our body's state, for example the positions and velocities of our body segments, is fundamental for accurate motor control. However in the SCI population this requirement (i.e. proprioceptive feedback) is no longer available.

S Hotz-Boendermaker, M Funk, P Summers, P Brugger, MC Hepp-Reymond, A Curt and SS Kollias. **Preservation of motor programs in paraplegics as demonstrated by attempted and imagined foot movements.**. *Neuroimage,* submitted.

The task of Study 2 consisted of a simple dorsal and plantar flexion. It was first executed resp. attempted to move in SCI patients, followed by imagination of the same movement. In addition, the patient group underwent a structured interview designed for evaluating static phenomena, paresthesias and movement sensations (see Appendix A). Study 2 revealed distinct activation patterns for movement attempt and for motor imagery in the SCI patients similar to the data of the control group. However, the SCI patients showed stronger activation in regions important for maintaining sensorimotor representations or/and enhanced attention. The retained integrity of movement attempt and motor imagery networks in SCI patients suggests that these patients can still dispose of the full motor program for foot movements, however with adaptations to the altered physical situation. Theories of motor control postulate that the brain uses internal models of the body state to control movements accurately The deprivation of proprioceptive feedback on limb position might have been replaced by other sensory modalities (i.e. visual input).

Author contributions. SHB, PS, MCHR, SSK and AC conceived and designed the experiments. AC and SHB recruited the patients. SHB, MF and PS performed the experiments. SHB and MF designed and conducted the structured interview. SHB analyzed the data.

2.4.3. FMRI study on foot movement observation in SCI patients (Study 3)

The purpose of Study 3 was to generate by the means of the observation/execution system an internal representation of an observed foot movements in complete long-term SCI patients.

S Hotz-Boendermaker, MC Hepp-Reymond, M Funk, P Summers, P Brugger, A Curt and SS Kollias. **Linked networks for execution, imagination and observation of hand movements as confirmed through adaptive processes in paraplegia.** *(in prep.)*

The tasks in Study 3 consisted of an executed foot movement with the subsequent observation the same videotaped movements in the next sequence. The videotaped foot movements were back-projected onto a screen in the scanner room and presented to the subjects over a mirror. Observation of foot movements in Study 3 activated the mirror system accordingly to the theory in both the healthy controls and the SCI patients. This

result confirmed the SCI patient's ability to generate an internal movement representation as disclosed in the controls.

Author contributions. SHB, PS, PB, MCHR, SSK and AC conceived and designed the experiments. AC and SHB recruited the patients. SHB, MF and PS performed the experiments. SHB and MF designed and conducted the structured interview. SHB analyzed the data.

3. OWN CONTRIBUTIONS

3.1. Study 1: What Disconnection Tells about Motor Imagery: Evidence from Paraplegic Patients

3.1.1. Abstract

Brain activation during motor imagery has been the subject of a large number of studies in healthy subjects, leading to divergent interpretations with respect to the role of descending pathways and kinesthetic feedback on the mental rehearsal of movements. We investigated patients with complete spinal cord injury (SCI) to find out how the complete disruption of motor efferents and sensory afferents influences brain activation during motor imagery of the disconnected feet. Eight SCI patients underwent behavioral assessment and functional magnetic resonance imaging. When compared to a healthy population, stronger activity was detected in primary and all non-primary motor cortical areas and subcortical regions. In paraplegic patients the primary motor cortex was consistently activated, even to the same degree as during movement execution in the controls. Motor imagery in SCI patients activated in parallel both the motor execution and motor imagery networks of healthy subjects. In paraplegics the extent of activation in the primary motor cortex and in mesial non-primary motor areas was significantly correlated with the vividness of movement imagery, as assessed by an interview. The present findings provide new insights on the neuroanatomy of motor imagery and the possible role of kinesthetic feedback in the suppression of cortical motor output required during covert movements.

3.1.2. Introduction

Motor imagery (MI) is defined as mental rehearsal of a motor act without any overt movement execution (ME*)*. There is strong evidence that MI can modify and even improve motor performance (Gandevia, 1999), and many studies have sought to delineate its underlying mechanisms and identify its cortical correlates. Comparisons of brain activation patterns acquired by positron emission tomography and functional magnetic resonance imaging (fMRI) during ME and MI have shown that several cortical and subcortical regions are specifically engaged during MI (Roland *et al.*, 1980; Stephan *et al.*, 1995; Deiber *et al.*, 1998; Luft *et al.*, 1998; Lotze *et al.*, 1999, Gerardin *et al.*, 2000; Johnson *et al.*, 2002;

Lafleur *et al.*, 2002; Hanakawa *et al.*, 2003). These regions include at the cortical level the supplementary motor (SMA), the pre-SMA, rostral prefrontal, premotor and posterior parietal areas, and subcortically the anterior portion of the putamen, the caudate nucleus bilaterally and posterolateral aspects of the anterior cerebellar hemispheres. The majority of these regions also participate in motor preparation (Deiber *et al.*, 1996). Some authors emphasize that certain regions are active during both covert motor acts and overt movements (Stephan *et al.*, 1995; Gerardin *et al.*, 2000). To them belong the superior parietal and lateral premotor areas, mainly posterior parts of the putamen and anterior and more medial aspects of the cerebellum. Several investigations have even reported involvement of the primary motor cortex during MI, but with lower levels of activation when compared to ME (Porro *et al.*, 1996; Roth *et al.*, 1996; Lotze *et al.*, 1999; Nair *et al.*, 2003). The participation of the sensorimotor cortex in MI is also supported by electroencephalographic, magnetoencephalographic and TMS investigations (Beisteiner *et al.*, 1995; Schnitzler *et al.*, 1997; Abbruzzese *et al.*, 1999).

The possibility that the neuronal network involved in ME may also be active during MI raises a number of issues addressing the origin of this activation. (i) The central nervous system may run a template of the movements without activating the motor plant, sharing partly overlapping networks for motor preparation and execution. This model is favored by cognitive neuroscientists (Jeannerod, 1994; Jeannerod and Frak, 1999; Fadiga *et al.*, 1999). (ii) Mental rehearsal may partially activate the descending corticospinal pathway, the spinal machinery and effector muscles (Gandevia *et al.*, 1993, 1997). In line with this hypothesis are the observations that spinal circuits are activated by transcranial magnetic stimulation (TMS) in a similar manner during MI and ME (Bonnet *et al.*, 1997; Kiers *et al.*, 1997; Rossini *et al.*, 1999). This finding, however, is challenged by other studies, showing modulation of the motor cortical excitability without evoking descending volleys to the spinal cord (Kasai *et al.*, 1997; Yahagi and Kasai, 1998; Hashimoto and Rothwell, 1999; Abbruzzese *et al.*, 1999). (iii) Activation during MI may be caused by plastic changes in cortical excitability induced by the absence of somatosensory, in particular kinesthetic, feedback in covert movements. Indeed, recent results (Ziemann *et al.*, 1998) have revealed an increase of motor cortical excitability after experimental deafferentation, confirming thus earlier findings (Brasil-Neto *et al.*, 1993). (iv) The inconsistent and less significant primary motor cortex activation during MI as compared to ME may be explained by the cortico-

cortical inhibition required to prevent activation of the peripheral motor apparatus during MI (Porro *et al.*, 1996).

The present study was designed to answer these issues by investigating brain activation in paraplegic patients during MI with fMRI. Patients with traumatic spinal cord injury (SCI) suffer an acutely acquired disconnection of efferent motor and afferent sensory pathways between the lower body parts and the cortical and subcortical structures. The paraplegic condition rules out any subliminal activation of the spinal cord and motor plants from cortical and subcortical origin. Enhanced cortical excitability conveyed by the transient loss of afferent somatosensory input can be also dismissed, but plastic changes due to long-term deafferentation could be revealed. We thus made two predictions. First, the brain activation patterns in the SCI patients during MI should merely reflect the central nervous dynamical circuit for motor behavior, or template of movements. Second, the comparison between the cortical and subcortical activations in healthy subjects and those in paraplegics may give a cue as to the central sources of movement suppression during MI, and/or the plastic changes induced by the paraplegic condition.

Essential to the goals of the present study was the behavioral assessment of the SCI patients. Specifically, we quantified the patients' ability to imagine movements of their disconnected foot, to ensure that brain activity was related to MI and not to an attempt to move (Shoham *et al.* 2001; Sabbah *et al.*, 2002). According to Decety and Boisson (1990) and Gandevia *et al.* (1993), SCI patients are still able to mentally rehearse movements of their disconnected limbs and report movement duration and sensation of effort in the same way as healthy controls. These similarities provide the foundation for comparing brain activation patterns related to MI in SCI patients with those of a healthy population. Furthermore, the quantification of MI vividness allows correlating individual ratings with the quantitative fMRI findings, and thus provides additional characterization of the central structures subserving MI.

3.1.3. Material and Methods

3.1.3.1. Subjects

Eight paraplegic patients (three female, five male, mean age 31.3 years, range 22–43 years) participated in this study. Chapman and Chapman's (1987) handedness inventory revealed

clear right-hand dominance in all patients (mean score 14.0). The mean period following traumatic SCI was 32 months (range 4–76 months). Only patients with chronic SCI were included so that the influence of long-term deafferentiation on the ability to internally generate motor images could be investigated. All suffered from complete SCI between T3 and L1, as assessed clinically with the impairment scale of the American Spinal Injury Association (ASIA: A; Maynard *et al.*, 1997) and electrophysiologically by motor evoked potentials (MEP) in the anterior tibial muscle after transmagnetic stimulation (TMS) and by recording of somatosensory evoked potentials (SEP) by stimulation of the tibial nerve. Individual clinical data can be found in Curt *et al.* (2002). None had suffered a brain lesion, and all had a normal Glasgow Coma Scale (Teasdale and Jennett, 1974) following SCI. Exclusion criteria included medical or mental illness, substance abuse, and use of medication known to alter cognitive and neurological activity. To assess MI, a structured interview on phantom sensations (Brugger and Regard, 1998; Brugger *et al.*, 2000) was carried out by telephone within 4 weeks after the fMRI sessions. It comprised questions regarding presence, quality, intensity and modifiability of various sensations referred to the disconnected body parts (see Supplementary Material). Among the questions, one was specifically designed for the present study. Participants were asked to take a reclined position and imagine, eyes closed, to perform repetitive flexion/extension movements of the right foot during 30 s. The rate of imagined movements was not specified, but it was stressed that the ‘speed of imagined movements should be such that continuous mental monitoring would be guaranteed’. On a seven-point scale (sent to each participant 1 week before the interview), the SCI patients were then required to rate the vividness of these imaginary movements from absent (0) to high (7).

Eight right-handed (mean score 13.1), healthy subjects (four female, four male, mean age 29.6 years, range 26–36 years) with no history of neurological or psychiatric illness were recruited as controls. The ability to kinesthetically imagine movements of their feet was assessed by the Vividness of Motor Imagery Questionnaire (VMIQ; Isaac *et al.*, 1986). Only subjects who had reached the score of 60 or less (possible range, 24–120; best score, 24), thus fulfilling the criterion for vivid kinesthetic MI ability, were included in this study (mean score, 43; range, 38–51). The study was approved by the Ethics Committee of the Medical Faculty of the University of Zurich, Switzerland. Written informed consent was obtained from all participants according to the Declaration of Helsinki.

3.1.3.2. FMRI Tasks

The control subjects were instructed to execute repetitive flexion and extension movements of the right foot at the ankle at a rate of approximately 0.5 Hz. The SCI patients were familiar with the 0.5 Hz rhythm as they had to perform upper limb movements at this rate during the same session prior to the MI experiment (Curt *et al.*, 2002). For the MI condition, both controls and SCI patients were required to imagine themselves performing the same movements without actually executing them. To ensure proper task execution in both SCI patients and healthy subjects, each task was practiced first outside and then inside the magnet bore prior to the scanning procedure. The experimental design consisted of three repetitions of 30 s periods of rest alternating with 30 s periods of ME (controls) or MI (controls and SCI patients). The beginning and end of each task period was verbally transmitted over the scanner intercom system. The experimenters visually controlled the subjects during the task performance and checked for potential movements in the trunk and lower limbs during MI. Assessment of surface EMG during fMRI still lacks the sensitivity to detect small and undesired movements due to gradient-induced artifacts (Dai *et al.*, 2001) and was not performed in this study. Overt motion was never observed during the MI task. In the control population EMG recordings were performed outside of the scanner in a separate experiment after the scanning, to only include subjects without any EMG activity during MI. In an open interview after the fMRI, all participants reported that they had been able to perform the MI task. During the experiments, all individuals had their eyes closed and the light was dimmed in the scanner room.

3.1.3.3. Imaging Procedures

Imaging was carried out on a 1.5 T whole body scanner (Signa Horizon; Echo-speed LX General Electric Medical Systems, Milwaukee, WI) equipped with a standard product transmit-receive head coil. T_1-weighted whole-brain anatomical reference volume data with an isotropic spatial resolution of 1.2 mm were acquired with a 3D spoiled gradient echo sequence [T_E (echo time) = 9 ms, T_R (repetition time) = 50 ms]. fMRI was conducted using a gradient-echo echo-planar pulse sequence (T_E = 40 ms, T_R = 3750 ms, flip angle 90°) sensitive to blood oxygen level dependent (BOLD) signal. Thirty contiguous, axial slices with a slice thickness of 4 mm covering the entire brain were acquired. The imaging matrix

consisted of 128 x 96 data points resulting in a rectangular field-of-view of 256 x 192 and a nominal in-plane resolution of 2 x 2 mm. Series of 48 sequential volumes were acquired for each experiment.

3.1.3.4. fMRI Data Analysis

The data analysis and postprocessing were performed offline as follows. To minimize artefacts due to residual head motion, functional volumes were realigned using a rigid-body registration algorithm (Woods *et al.*, 1998). Subsequently, data were spatially filtered using a 3D Gaussian convolution kernel of 4 mm at full-width half-maximum (FWHM). For single subject analysis, normalization into Talairach space was not performed. For the group analysis, all volumes were registered to the Montreal average volumetric data set aligned on the Talairach stereotactic coordinate system (Collins *et al.*, 1994). The statistical analysis of all fMRI data was based on a linear model with correlated errors and was carried out for each data set (Worsley *et al.*, 1996; http://www.math.mcgill.ca/keith/fmristat). The design matrix of the linear model was first convolved with a gamma hemodynamic response function (Glover, 1999). Drift was removed by adding polynomial covariates in the frame times, up to degree 3, to the design matrix. Resulting effects and their standard errors were determined on a voxel by voxel basis. In a second step, sessions were combined using a mixed effects linear model with standard deviations taken from the previous analysis (Worsley *et al.*, 1996). A random effects analysis was performed by first estimating the ratio of the random effects variance to the fixed effects variance, then regularizing this ratio by spatial smoothing with a 15 mm FWHM filter. The variance of the effect was then estimated by the smoothed ratio multiplied by the fixed effects variance to achieve higher degrees of freedom. The resulting *t*-statistic images were then thresholded using the minimum given by a Bonferroni correction and random field theory (Worsley *et al.*, 1996). The threshold for significant activation was $P < 0.05$ with a corresponding *Z*-value of 4.85, corrected for multiple comparisons. For each activation cluster, the volume of activation, the maximum signal intensity, and the geometrical center of gravity were determined and the location in Talairach coordinates retained. Homogenous distribution in each cluster was assumed for the center of gravity calculation; therefore, all voxels above the significant threshold were weighted uniformly. The anatomical boundaries of all segmented areas were defined

according to a previous publication (Kollias *et al.*, 2001). Cerebellar lobule identification was based on the nomenclature of Larsell and Jansen (1972).

3.1.3.5. Correlation between Vividness of MI, Brain Activation and Time since SCI

For the SCI patients, non-parametric Spearman rank order correlation coefficients were computed for all segmented areas between the MI vividness ratings and quantitative aspects of the BOLD signal (maximum *t*-value and volume of activation). Additional Spearman rank order correlation coefficients were calculated between the time since SCI and the degree of activation in all segmented areas, and between the time since SCI and the individual vividness ratings. In the healthy population, no correlation coefficients were computed since only subjects with similar VMIQ scores were included (see Materials and Methods).

3.1.4. Results

The patterns of activation were analyzed for both populations to identify the main fields involved in MI, in ME, and the differences between healthy subjects and SCI patients. Table 1 lists all functional areas activated by execution and imagination of foot movements, the corresponding cytoarchitectonic regions, cluster volumes, Talairach coordinates of their COGs, and maximum *t*-values of the group analyses versus rest (contrasts i, ii and iii).

3.1.4.1. Group results

(i) Execution of Right Foot Movements Contrasted to Rest in Healthy Controls

Activation was detected in the primary motor foot area, in the primary somatosensory (S1), dorsal premotor (PMd) and superior parietal areas contralaterally, and in the SMA and cingulate motor areas (CMA) bilaterally (Fig. 1a, b). No activation in the basal ganglia or in the thalamus was detected (Fig. 1c). Additional activation was present in the ipsilateral anterior cerebellar hemispheres (Larsell lobules II–III, (Fig. 1d). and Table 1.

(ii) Imagination of Right Foot Movements Contrasted to Rest in Healthy Controls

MI of the foot in the controls elicited activation bilaterally in the SMA, CMA, ventral premotor (PMv), PMd, superior parietal and prefrontal areas, secondary somatosensory cortex (S2) and in contralateral (left) inferior parietal areas (Fig. 1e-g, and Table 1). The

group analysis did not reveal any activity in the primary motor cortex, the basal ganglia, or the thalamus (Fig. 1e,g). Bilateral cerebellar activation was located more posteriorly and laterally in Larsell lobules H VIIA of the anterior hemispheres (Fig. 1h).

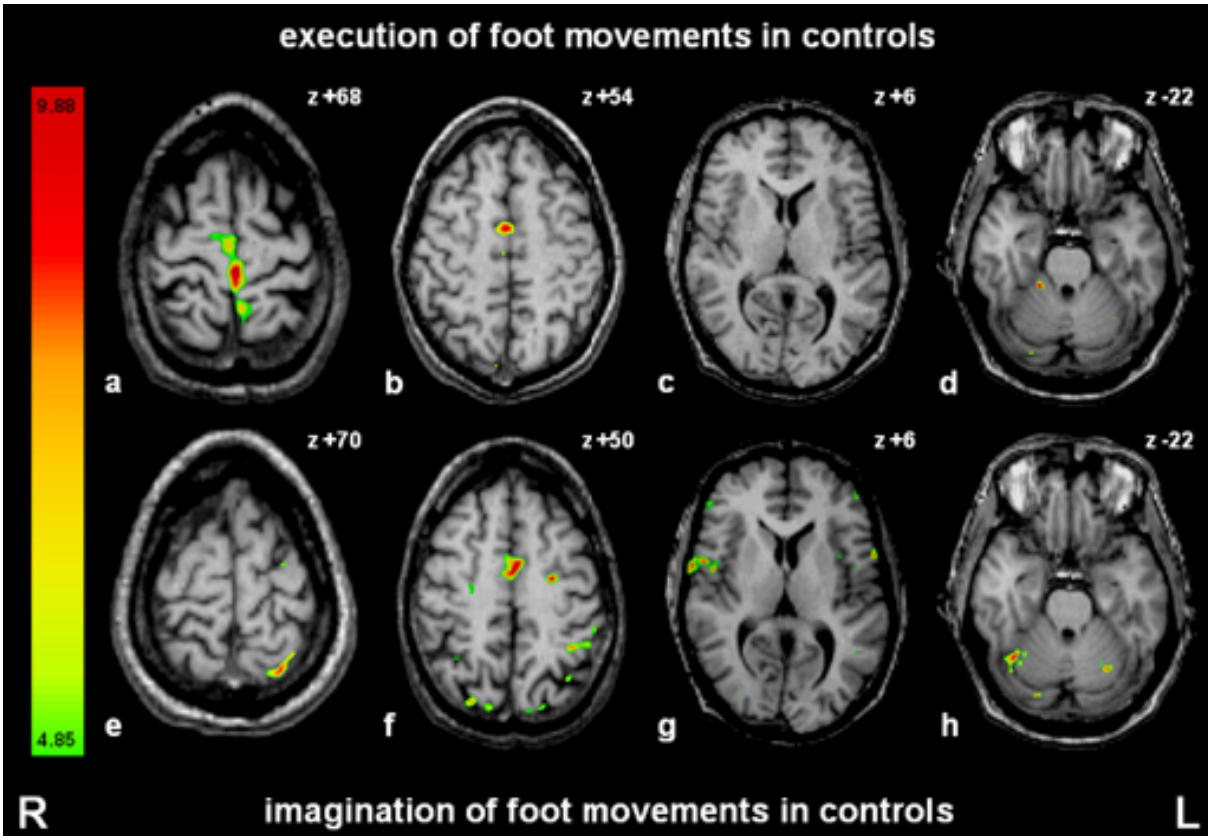


Figure 1. Activation patterns during execution (a–d) and imagination (e–h) of right foot movements in the healthy controls (group analysis). Movement execution activated the contralateral primary motor and somatosensory foot area, the SMA and CMA bilaterally (a, b) as well as the ipsilateral anterior cerebellum (Larsell lobules II–III, d), while activation in thalamus and basal ganglia was absent (c). Imagination of right foot movements activated CMA, PMd, PMv, parietal, and prefrontal areas bilaterally (e–g). No activity was detected in the primary motor cortex, in the basal ganglia or the thalamus (e, g). Cerebellar activation was bilateral, more posterior and lateral, located in Larsell lobules H VIIA (h). Right side on the image corresponds to left hemisphere. z-Coordinates corresponding to Talairach space (Collins et al., 1994). Numbers in the color bar correspond to t-values.

(iii) Imagination of Foot Movements Contrasted to Rest in SCI Patients

This group analysis revealed a significant BOLD signal in the contralateral primary motor and S1 foot representation (Fig. 2a, b). The clusters of activation showed no shift into the hand or trunk primary motor area and no spatial spread to adjacent cortical regions. The Talairach coordinates of primary motor cortex activation were similar to those of healthy

Table 1: Talairach coordinates, maximum t-values, and activation volumes for motor execution and imagery.

functional area		motor execution in controls					motor imagery in controls					motor imagery in paraplegics				
(Brodmann area)		x	y	z	max. t-value	volume (mm3)	x	y	z	max. t-value	volume (mm3)	x	y	z	max. t-value	volume (mm3)
M1	right															
(BA 4)	left	-3	-28	67	10.1	2776						-4	-28	71	10,1	2904
S1	right											7	-37	70	7,3	39
(BA 1,2,3)	left	-8	-38	70	7.8	832						-11	-43	71	8,9	1328
SMA	right	5	-14	67	6.8	128	8	-6	76	6,3	112	5	-7	65	10,2	2416
(BA 6)	left	-4	-20	72	6	608	-1	-7	76	6,1	96	-3	-10	65	12,9	2848
pre-SMA	right											6	4	64	8,7	1248
(BA 6)	left											-4	4	68	8,1	720
PMd	right											51	2	51	6,5	96
(BA 6)	left	-15	-22	68	8.1	368	-25	-8	60	6	128	-39	-3	56	6,5	512
PMv	right						56	2	7	6,5	800	58	12	10	7,2	512
(BA 6,44,45)	left						-59	8	11	5,8	144	-55	8	14	6,2	320
CMA	right	-1	-6	50	5.6	80	2	-3	52	5,5	96	4	8	41	7,1	1056
(BA 6,24)	left	3	-6	51	5.7	112	-1	0	51	6	432	-6	-3	41	7,9	1088
superior	right						27	-75	52	5,1	48	20	-30	64	5,2	80
parietal (BA 7)	left	-12	-47	69	7.5	818	-16	-65	62	7,4	832	-44	-47	50	6,7	1104
inferior	right											57	-36	42	5,7	144
parietal (BA 40)	left						-43	-44	56	6,3	368	-57	-32	41	5,9	144
S2	right						65	-31	31	6,5	310	56	-32	34	6,4	528
(BA 40,43)	left						-57	-34	34	6,7	432	-63	-22	20	5,4	96
prefrontal areas	right						51	40	4	5,9	144	50	37	17	6,7	836
(BA 46)	left						-48	45	8	5,1	80	-48	43	12	6,7	352
thalamus	right											14	-11	16	6,3	592
	left											-11	-12	15	6,9	1008
putamen	right											21	3	12	6,2	304
	left											-26	-10	7	5,8	608
caudate nucleus	right											20	-7	24	6,2	272
	left											-16	-12	24	6,2	448
cerebellum	right	20	-40	-24	6.2	608						16	-45	-22	9,3	2240
Larsell II-III	left											-11	-45	-20	6	496
cerebellum	right						39	-57	-24	5,2	96	36	-63	-26	8	1296
Larsell H VIIA	left						-30	-65	-28	5,9	336	-32	-67	-28	7	1600

subjects during motor execution (Table 1). In addition, bilateral fields of activation were present in SMA, pre-SMA, CMA, PMd, PMv, superior and inferior parietal regions, S2, and the insular and prefrontal cortex (Table 1). Strong bilateral subcortical activation was also detected in the putamen, caudate nucleus and thalamus (Fig. 2d,e). In the cerebellum activation was found in Larsell lobules II–III mainly ipsilaterally, and symmetrically in both Larsell lobules H VIIA (Fig. 2c). In summary, these data suggest that the cortical and subcortical activation patterns in the SCI patients during MI correspond to the sum of the activations obtained during both ME and MI in healthy controls.

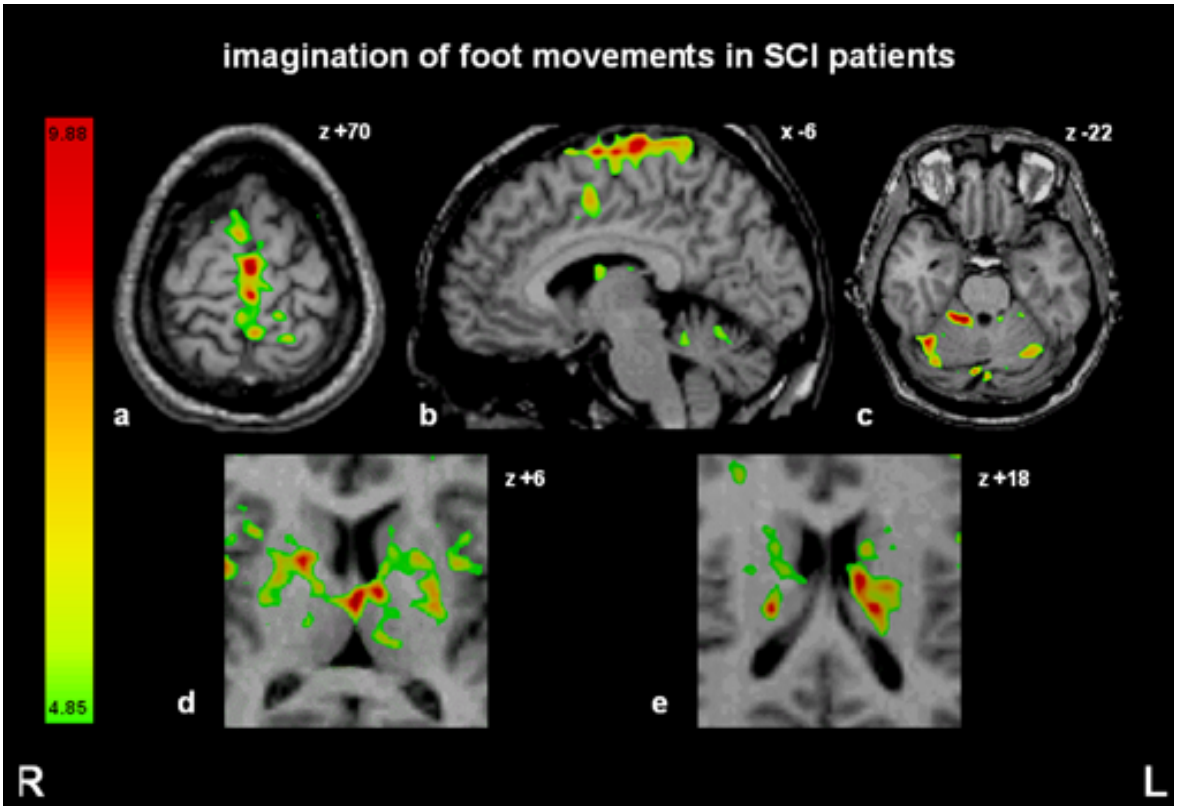


Figure 2. Activation patterns during imagination of right foot movements in the SCI patients contrasted with rest (group analysis). The contralateral primary motor foot area was strongly activated (a, b). Further activity is seen in the SMA, pre-SMA and CMA bilaterally (a, b). Cerebellar activation was present in Larsell lobules II–III, mainly ipsilaterally, and symmetrically in both Larsell lobules H VIIA (c). Strong subcortical activation occurred in the bilateral putamen, caudate nucleus, and the thalamus (d, e). Same conventions as in Figure 1.

(iv) Imagination of Foot Movements: Contrast between SCI Patients and Controls

To test whether MI in SCI patients elicited the same degree of activation in the same regions as MI in controls, data obtained in healthy subjects were subtracted from those in SCI patients. The resulting fMRI maps showed activation in all cortical and subcortical regions

described above (iii). They include the contralateral primary motor and S1 foot representation, and bilaterally the SMA, pre-SMA, CMA, PMd, PMv, superior and inferior parietal regions, S2, and the insular and prefrontal cortex (Fig. 3a, b). Further activation was present in the putamen, caudate nucleus, and thalamus bilaterally, in the cerebellum in Larsell lobules II–III ipsilaterally, and symmetrically in both Larsell lobules H VIIA (Fig. 3c-e). The Talairach coordinates of the COG of these regions are listed in (Table 1). This group contrast therefore revealed that the degree of activation in all cortical and subcortical regions active during imagination of foot movements (contrasted with rest, iii) was significantly higher in the SCI patients than in the controls.

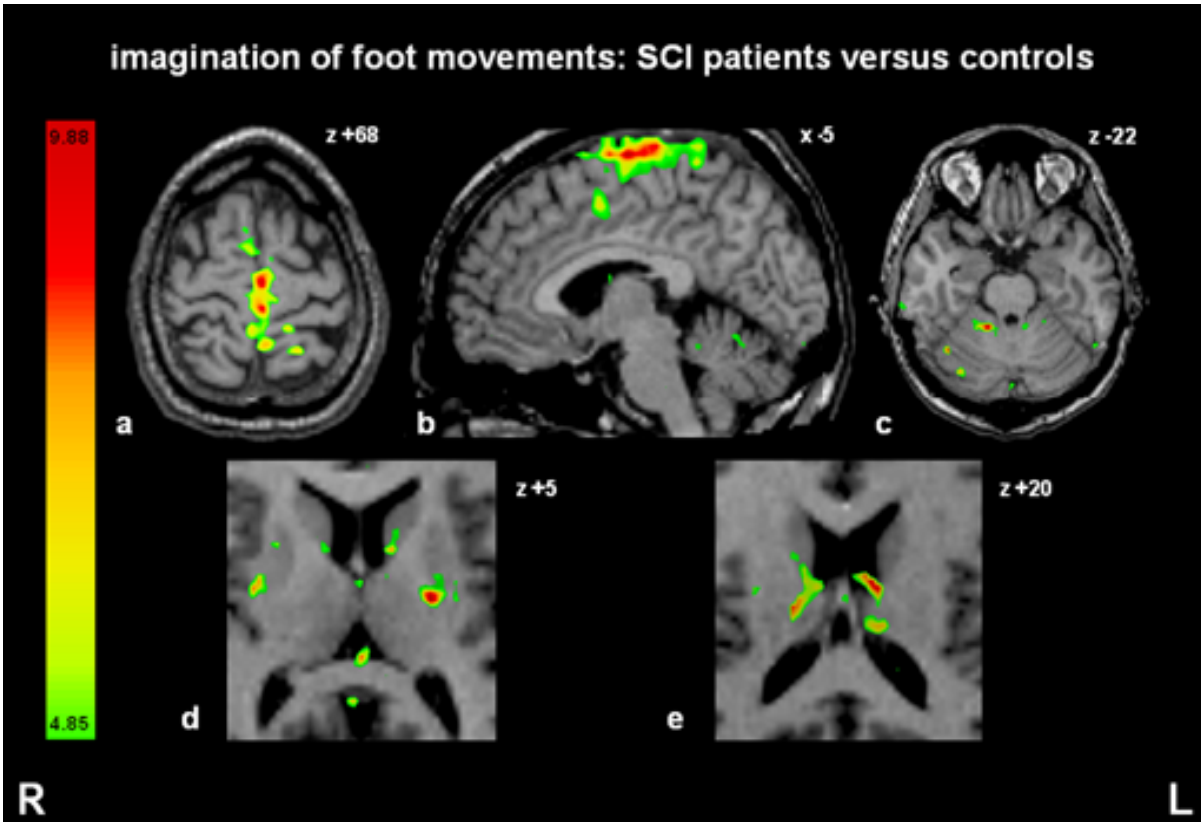


Figure 3. Activation patterns during imagination of right foot movements in the SCI patients contrasted to controls (group analysis). This contrast revealed activation foci in the same regions as shown in Figure 2 but to a lesser degree. These included the contralateral primary motor and somatosensory foot area, SMA, pre-SMA and CMA bilaterally (a, b). Subcortical activation was present in the cerebellum (Larsell lobules II–III and Larsell lobules H VIIA), and in the bilateral putamen, caudate nucleus, and the thalamus (c–e). Same conventions as in Figure 1.

(iv) Imagination of Foot Movements: Contrast between Controls and SCI Patients

As MI in healthy subjects requires suppression of the peripheral motor apparatus, the subtraction of the MI SCI data from the MI healthy control data should disclose regions specifically involved in MI in the controls. However, this subtraction did not reveal any

significant cortical or subcortical activation foci. This demonstrates that no region can be assigned to such a suppression during MI in healthy subjects.

(vi) Contrast between Imagination in SCI Patients and Execution in Controls

The enhanced activity revealed in previous contrasts (iii and iv) suggests that MI in SCI patients activated central structures in a similar way as ME in controls. To further test this observation, we subtracted the ME data of healthy subjects from those obtained in paraplegics during MI. Main result was that the contralateral primary motor cortex activation during ME was completely subtracted out. Significant activations resulting from this contrast were located in all other cortical areas and subcortical regions listed above (iii) and in (Table 1). This finding demonstrates that the degree of activation was significantly higher in the SCI patients during MI than in the controls during ME, in all the regions except the primary motor cortex.

(vii) Contrast between Execution in Controls and Imagination in SCI Patients

It was expected that the subtraction of the MI SCI data from the ME control data would reveal some foci of increased activation in the controls during ME. However, no significantly increased activation in any area could be detected. Together with the previous contrast (vi) this finding confirms that the contralateral primary motor cortex was activated in the controls to the same degree during ME as in the SCI patients during MI (volumes 2776 versus 2904 mm3, both maximum *t*-values 10.1).

3.1.4.2. Results of Individual Subjects

In the single subject analysis the correspondence between anatomical structures and the BOLD signals can be determined with higher precision as the single subject data are not normalized into Talairach space, a procedure with inherent inaccuracies. This was of particular interest for the primary motor cortex, S1, and subcortical structures, where the group analysis may have failed to detect activation during MI due to a low signal-to-noise ratio. The results are presented in Table 2, which lists for each region the number of SCI patients with detected activation during MI and of healthy subjects during ME and MI

Table 2: Number of controls and SCI patients with activation clusters during execution and imagination of right foot movements.

functional area (Brodmann area)	hemisphere	controls (n=8) motor execution	motor imagery	SCI patients (n=8) motor imagery
M1 (4)	left / right	8 / 0	4 / 0	8 / 0
SMA (6)	left / right	8 / 7	7 / 8	7 / 7
pre-SMA (6)	left / right	0 / 1	4 / 5	3 / 5
PMd (6)	left / right	6 / 4	7 / 4	6 / 6
PMv (6)	left / right	6 / 4	8 / 8	8 / 8
CMA (6,24)	left / right	7 / 6	3 / 4	6 / 6
S1 (1,2,3)	left / right	8 / 1	2 / 0	7 / 1
superior parietal (7)	left / right	6 / 4	7 / 4	5 / 6
inferior parietal (40)	left / right	4 / 7	4 / 4	7 / 8
S2 (40,43)	left / right	6 / 8	5 / 5	7 / 8
prefrontal areas (9,10,11,46)	left / right	0 / 0	7 / 5	7 / 8
thalamus	left / right	0 / 4	1 / 5	6 / 6
putamen	left / right	4 / 3	2 / 5	8 / 8
caudate nucleus	left / right	0 / 0	2 / 4	6 / 7
insula	left / right	6 / 4	6 / 2	6 / 6
cerebellum				
Larsell lobule II-III	left / right	2 / 8	0 / 1	4 / 5
H VIIA	left / right	4 / 2	7 / 7	6 / 6

Deviations from the group analysis were only found for the healthy controls. Inconsistent activation was present in the putamen, thalamus and cerebellum during ME and in the pre-SMA, thalamus and cerebellum during MI. Activation of the contralateral primary motor foot area during MI occurred in four of the eight controls (mean volume 586 ± 243 mm3) and in two in S1 (mean volume 197 ± 64 mm3). In contrast, the analysis of the individual SCI patients' data during MI revealed the same fields of activation as the group analysis and did not disclose any additional one. Striking was the clear BOLD signal in the contralateral primary motor cortex in all eight SCI patients and in S1 in seven of them. These activation

clusters were located in the primary motor and S1 foot representations, without any shift or spread into hand or trunk representations or other adjacent regions. Moreover, the basal ganglia, thalamus and cerebellum were consistently bilaterally activated. In the SCI patients, the degree of activation in the primary motor, non-primary motor and subcortical regions did not correlate significantly with the individual delays since SCI (all Spearman rho ≤0.553, $P \geq 0.15$).

3.1.4.3. Correlations between MI Vividness Scores, Brain Activation and time since SCI

Of the seven SCI patients interviewed (one patient refused to take part in the interview), all reported the presence of various phantom sensations. In particular, kinesthetic MI of their deafferented right foot was spared, as indicated by non-zero ratings of the vividness of imagined movements for each individual participant. The mean vividness rating for the imagined foot movements during the 30 s period was 3.7 (SD 1.6). Correlation coefficients were computed between the MI vividness ratings and quantitative aspects of the BOLD signal (maximum *t*-values and volumes of activation) in all regions with significant activation.

In the primary motor cortex, the individual MI ratings were significantly correlated with the maximum *t*-values (rho = 0.873, $P < 0.01$, see Fig.4) and a positive trend found with the activated volumes (rho = 0.750, $P = 0.05$). In several non-primary motor areas, the MI vividness ratings correlated significantly with the maximum t-values and/or volumes of activation. Positive correlation coefficients were found with the maximum *t*-values in the left SMA (rho = 0.982, $P < 0.01$, Fig.4) and in the right pre-SMA (rho = 0.856, $P < 0.05$), and with the activated volumes in the left pre-SMA (rho = 0.837, $P < 0.05$, Fig.4) and left CMA (rho = 0.909, $P < 0.01$). For the latter area, the correlation coefficient was also significant with the maximum *t*-values (rho = 0.782, $P < 0.05$). For some of these regions, the scatter diagrams of the BOLD signal values as a function of MI vividness scores are displayed in Figure 4. The BOLD signal in the other cortical areas and in all subcortical regions did not correlate with the individual MI scores (all rho-values ≤0.514, $P \geq 0.09$).

There was no significant correlation between the individual vividness ratings in the SCI patients and the delays since SCI (all Spearman rho ≤0.503, $P \geq 0.12$).

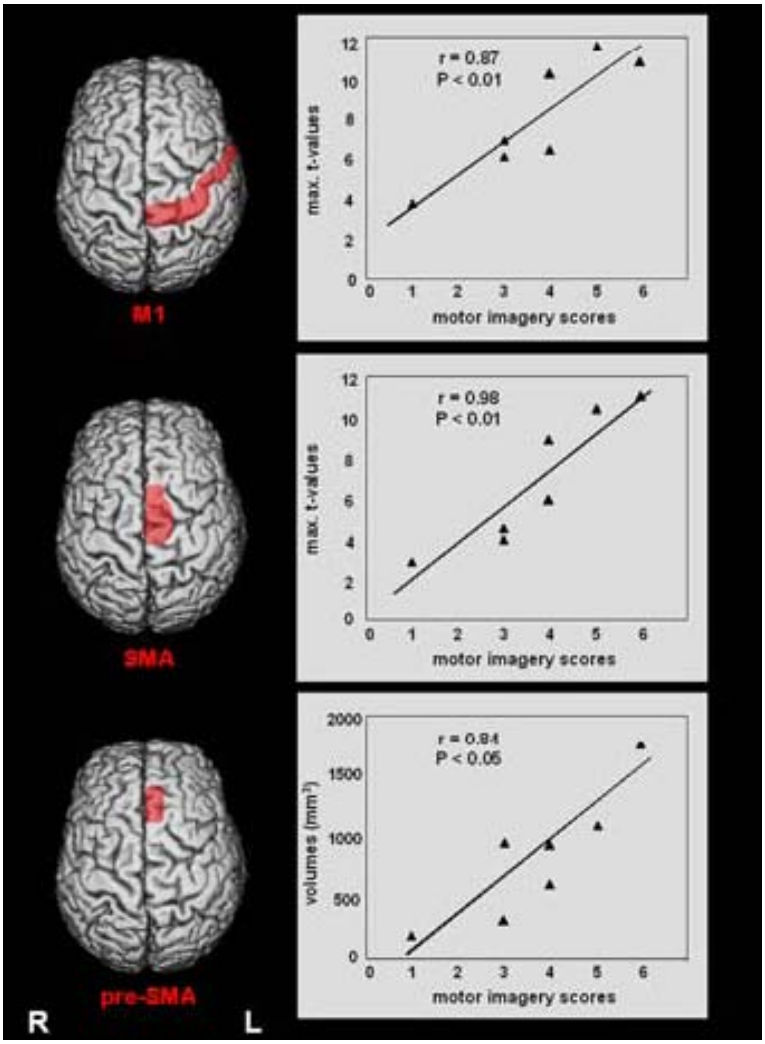


Figure 4. Scatter diagrams displaying the degree of activation in three cortical areas as a function of the vividness scores of motor imagery in the paraplegics. The individual motor imagery scores correlated significantly with the maximum t-values in the contralateral primary motor cortex (upper row) and left SMA (middle row), and with the volumes of activation in left pre-SMA (lower row).

3.1.5. Discussion

The present study reports for the first time the occurrence of strong and consistent brain activation in a large number of cortical and subcortical regions in SCI patients during MI of their disconnected feet. MI in SCI patients recruited in parallel both the ME and MI networks detected in healthy subjects, with an additional enhancement in the degree of activation. The contralateral primary motor and somatosensory foot representations were consistently activated in SCI patients, in the same location and to the same degree as in controls during ME. Both the group and the individual analysis revealed foci with unexpectedly strong BOLD signal in the putamen, caudate nucleus,

thalamus, and cerebellum. A comparable consistency in subcortical activity was never documented in the healthy controls, neither during ME nor during MI. Finally, for the SCI patients the degree of brain activation in the primary motor cortex and in some non-primary motor areas was significantly correlated with the self-rated MI vividness.

3.1.5.1. Cortical and Subcortical Correlates of MI in Healthy Subjects

The most common view on MI based on neuropsychological and imaging data postulates that the mental representation of a motor act, its preparation, and actual execution involve similar brain areas (Jeannerod, 1994). The difference between covert and overt activity is manifested at the final motor output level, which must be actively suppressed during MI (Jeannerod and Frak, 1999). This model is supported by the behavioral literature which has reported remarkable parallels between MI and ME in healthy subjects, e.g. the similar amount of time needed to mentally complete a movement (Decety and Michel, 1989), the similar physiological responses associated with physical effort (Decety *et al.*, 1991), and the constraints of MI by the same physical laws that apply to ME (Sirigu *et al.*, 1996). This view is confirmed by the present findings in healthy controls, as several central structures were recruited in parallel during MI and during ME. These include bilaterally the medial and lateral premotor and superior parietal areas and, to a lesser degree, the contralateral primary motor cortex, the putamen and thalamus. At the same time, our results confirm the existence of the previously described more specialized network underlying MI, involving pre-SMA, prefrontal areas, inferior parietal cortex and, at the subcortical level, the head of the caudate nucleus and Larsell lobules VIIA of the cerebellum bilaterally (Lotze *et al.*, 1999; Gerardin *et al.*, 2000; Hanakawa *et al.*, 2003).

3.1.5.2.The Effect of SCI on the Activation Patterns during MI

Despite the large number of behavioral and imaging investigations on MI in healthy subjects only two studies have so far assessed brain activation in SCI patients during mental simulation of foot movements (Lacourse *et al.*, 1999; Sabbah *et al.*, 2002). Sabbah *et al.* (2002) reported inconsistent fMRI activation in the primary motor cortex and in some non-primary motor areas during self-paced MI of the foot in complete SCI patients. On the basis of qualitative comparisons these authors concluded that the MI activation patterns in SCI

patients only partly differed from those during ME in healthy subjects and during attempted movements in paraplegics. Lacourse *et al.* (1999), in an investigation with event-related potentials, reported that the biphasic waveforms appearing prior to and during a button press with the foot in controls were depressed in SCI patients imagining the same movement with their paralyzed limbs. Their conclusion was that chronic deafferentation in the SCI condition leads to changes in cortical activity during MI suggesting weakened inihibitory processes. Both studies are limited by the fact that they focused on selected cortical areas and did not address the high behavioral variability in the performance of MI in both healthy and patient populations.

The present investigation extends these studies in three important aspects. First, the level of primary motor and S1 activation in the SCI patients significantly exceeded that of the controls during MI and even equaled that occurring during the execution itself. Second, we found in the SCI patients strong correlations between the degree of activation in the primary motor cortex and in some non-primary motor areas and the vividness of MI. Third, the comparison with healthy controls revealed an enhancement of activity in the whole central motor neural network, including subcortical regions.

The high degree of activation during MI of the disconnected limbs suggests that some of the observed modifications may be caused by plastic changes, resulting from the chronic lack of somatosensory feedback. Changes in cortical excitability and reorganization in chronic deafferentated SCI patients have been demonstrated with TMS (Levy *et al.*, 1990; Topka *et al.*, 1991), and with fMRI (Corbetta *et al.*, 2002; Curt *et al.*, 2002) an increase of activation in the primary motor hand representation without any substantial reorganization of the gross somatotopy has been reported. In patients who had either recovered some motor function or had residual use of their body parts, volitional activation in the primary motor cortex occurred with only minimal somatotopical reorganization (Shoham *et al.*, 2001), in contrast to obvious modifications or spread to adjacent regions in S1 (Corbetta *et al.*, 2002). Effects of transient and long-term deafferentation on the organization and excitability of the motor and sensory cortex are, in contrast, very well documented after amputation in monkeys and humans (Florence and Kaas, 1995; Chen *et al.*, 1998; Ramachadran and Hirstein, 1998; Qi *et al.*, 2000) and during experimental deafferentation by ischemic nerve block in human (Schnitzler *et al.*, 1997; Ziemann *et al.*, 1998). In human, TMS investigations strongly suggest two processes: First, a transient enhancement of excitability with larger motor

evoked potentials in the muscles proximal to the ischemic block occurring immediately after experimental deafferentation (Ziemann *et al.*, 1998), and second, a decrease of the motor thresholds in the case of long-term deafferentation in amputees (Chen *et al.*, 1998). Both imply that reduction of intracortical inhibition is involved in plastic changes (Jacobs and Donoghue, 1991).

It is likely that plastic changes in cortico-cortical inhibition caused by the long-term absence of sensory input to the primary motor and somatosensory cortex are the main factor contributing to the strong cortical and subcortical activity disclosed in SCI patients during MI in the present investigation. The occurrence of primary motor cortex activation in amputees imagining movements of their phantom limbs shown by fMRI leads to similar conclusions (Ersland *et al.*, 1996; Lotze *et al.*, 2001).

3.1.5.3. What Disconnection Tells about MI

Our findings in complete SCI patients, without any remaining output to the spinal cord and any sensory feedback, provide strong evidence that MI, as a kinesthetic representation of action, is engaging a central machinery of movement (Jeannerod, 1994). This template includes most central motor structures as well as parietal and prefrontal areas bilaterally (Gerardin *et al.*, 2000), each participating to various degrees to execution and imagination (Hanakawa *et al.*, 2003).

The consistent and strong activation not only of the primary motor cortex, but also of S1 in SCI patients merits some further comments. In our healthy population, S1 activation was only detected at the individual level in two subjects and did not reach the significance level in the group analysis. The inconsistent recruitment of S1 in MI is not a new finding, but has been mentioned in a few fMRI studies (Porro *et al.*, 1996; Gerardin *et al.*, 2000). In our SCI patients, the activation clusters in the primary motor and somatosensory cortex were topographically clearly segregated, both in the individual as well as in the group analysis. They cannot be attributed to feedback from peripheral afferents as the SCI patients were completely paralyzed, and no movement could be detected during MI task performance. This activation rather suggests that the internal rehearsal of movements relies on a kinesthetic memory of the imagined body parts that may still access S1 as well as the primary motor cortex, even many years after SCI. In other sensory modalities, activation of sensory-specific cortex has been reported during retrieval of the sensory information (Frith and Dolan, 1997;

Nyberg *et al.*, 2000; Wheeler *et al.*, 2000; Gandhi, 2001). Therefore, the activation of the primary somatosensory and motor cortex may depend on strong top-down processes. The existence of corollary discharges, instructing S1 on the intended movements through cortico-cortical projections even in the absence of sensory input, could be a complementary explanation for the S1 activation during MI. Corollary discharges have been evoked in several situations (for a review, see McCloskey, 1981), and the activation of the primary motor cortex and other motor regions during MI could recruit S1 through such a mechanism.

It was expected that the comparison of MI in healthy and SCI individuals would provide some insight into the structures and processes involved in the volitional movement suppression required in healthy subjects during MI (Jeannerod and Frak, 1999). If specialized brain regions were directly involved in this suppression, the subtraction of the MI activation patterns in SCI patients from those in healthy subjects should disclose potential 'inhibitory' regions. This contrast did not reveal any additional activation in the controls and thus did not confirm an earlier finding of Deiber *et al.* (1998) according to which the inferior frontal cortex would be the region responsible for motor suppression in a visuomotor MI task. In how far inputs arising from the spinal cord and modulating cortical excitability in healthy subjects may play a role in the motor suppression is still an open issue. Investigation in patients only suffering from sensory neuropathy may answer this question.

3.2. Study 2: Preservation of motor programs in paraplegics as demonstrated by attempted and imagined foot movements

3.2.1. Abstract

Execution and imagination of a movement activate distinct neural circuits, partially overlapping in premotor and parietal areas, basal ganglia and cerebellum. Can long-term deafferented and deefferented patients still differentiate attempted from imagined movements? The attempted execution and motor imagery network of foot movements have been investigated in nine chronic complete spinal cord injured (SCI) patients using fMRI. Thorough behavioral assessment showed that these patients were able to differentiate between attempted execution and motor imagery. Supporting the outcome of the behavioral assessment, fMRI disclosed specific patterns of activation for movement attempt and for motor imagery. Compared with motor execution data of healthy controls, movement attempt in SCI patients revealed reduced primary motor cortex activation at the group level, although activation was found in all single subjects with a high variability. Further comparisons with healthy subjects revealed that during attempt and motor imagery SCI patients show enhanced activation and recruitment of additional regions in the parietal lobe and cerebellum that are important in sensorimotor integration, as well as in the prefrontal cortex. These findings reflect central plastic changes due to altered input and output and suggest that SCI patients may require additional cognitive resources to perform these tasks. The retained integrity of movement attempt and motor imagery networks in SCI patients demonstrates that chronic paraplegics can still dispose of the full motor programs for foot movements and that therefore, attempted and imagined movements should be integrated in rehabilitative strategies.

3.2.2.Introduction

The human motor system generates accurate movements, which are centrally stored and can be modified and retrieved under various conditions. The complexity of the processes involved in any motor action has led to concept that the central nervous system contains

internal models representing these processes and optimizing motor control (Kawato, 1999; Wolpert and Ghahramani, 2000). Among these models, forward models predict the relationship between issued motor commands and the resulting changes in the sensorimotor system, monitored by the reafferent sensory inflow which supplies information about the state of the body. In this context, patients with complete spinal cord injury (SCI) provide a unique human model for studying the effects of deafferentation on motor control, and on the sensorimotor system in general.

We have recently used functional magnetic resonance imaging (fMRI) to investigate the activation patterns during motor imagery in chronic SCI patients (Alkadhi et al., 2005). This study provided evidence that in this patient group motor imagery still engages the central machinery of movements as suggested by (Jeannerod, 1995). Studies in healthy subjects revealed that internal simulation of a movement induces similar physiological reactions as its execution (Decety and Jeannerod, 1995; Jeannerod and Decety, 1995). A number of imaging studies disclosed functional circuits shared by both movement execution and imagination (Jackson et al., 2001; Lafleur et al., 2002), although subtle differences in the localization of activation foci between the two tasks have also been reported (Stephan et al., 1995; Gerardin et al., 2000; Hanakawa et al., 2003; Nair et al., 2003).

While it is generally accepted that “overt” or executed motor behavior and “covert” or simulated behavior are intimately related (Jeannerod, 2001), the ability to physically execute a movement is not necessarily required for its mental performance. This is well recognized in patients with hemiplegia who are still able after a cerebrovascular insult to mentally move their limbs, even after years of disuse (Johnson, 2000; Johnson-Frey, 2004). In a case-study using fMRI, a woman with congenitally absent limbs was able to cortically command movements of her phantom limbs, suggesting that body parts that have never been physically

developed can be represented in sensory and motor cortical areas (Brugger et al., 2000). In the investigation of (Alkadhi et al., 2005), paraplegic patients mentally moving their paralyzed feet strongly activated brain areas corresponding to both the execution network, including the primary sensorimotor cortex, and the imagery network described in healthy subjects.

In complete SCI patients, both intended overt movements and covert movements remain without obvious motor responses. Therefore, only attempted (MA) and imagined (MI) movements can be compared. The ability of SCI patients to distinguish between attempted and imagined movements has up to now not been assessed assessed behaviorally and only a few imaging studies have investigated brain activity in these patients during attempted and gimagined movements of the disconnected body parts (Sabbah et al., 2002;Cramer et al., 2005). These investigations with heterogeneous patient groups reported reduced activation in primary and secondary cortical motor regions for both MA and MI, thus being at odd with our previous experience (Alkadhi et al., 2005).

To address this issue, we undertook further neuroimaging investigations in a homogeneous group of chronic paraplegics, all after at least two years post injury, with complete SCI lesions ascertained by standardized neurophysiological methods. We consider this time interval as a chronic state and thus, appropriate to investigate the influence of long-term deafferentiation on attempting to move the feet and generating mental images of the same movement. In addition, the ability of the patients to perform MI and MA and to distinguish between the two was quantitatively assessed. We expected that in SCI patients able to distinguish between MI and MA these two tasks will generate distinct brain activation patterns.

3.2.3. Material and Methods

3.2.3.1. Subjects

Nine paraplegic patients were recruited from the outpatient clinic of our institution (3 females, 6 males, mean age 35 years, SD 6). The Edinburgh handedness inventory revealed clear right hand dominance for all subjects. Table 1 gives the age, sex, etiology of the SCI, the level of complete motor deficit, and the time since SCI. For the nine patients the mean period following traumatic SCI was 9 years (range 2-20 years).

All had clinically complete motor SCI between Th3 and L3, as assessed with the impairment scale of the American Spinal Injury Association (ASIA, Maynard et al., 1997), transcranial magnetic stimulation (TMS), and somatosensory evoked potentials (SSEP, Curt and Dietz, 1999). All subjects had repeated clinical examinations and SSEP of the posterior tibial nerves and MEP (motor evoked potentials) of the anterior tibial muscles.

Table 1. Individual clinical and behavioral data for the SCI patients with means

Subject	Level of complete motor impairment / ASIA[1]	Age / Sex[2]	Time since injury (years)	Vividness of motor imagery (VQIM) [3]	Ability for attempted movement Intensity[4]	Frequency for attempted movemen[4]
S1	Th6/A	40/M	7	54	3	3
S2	L1/A	28/M	11	33	4	4
S3	Th5/A	42/M	20	24	5	5
S4	L3/B	29/M	2	26	6	6
S5	Th3/A	38/M	5	106	4	1
S6	Th6/A	29/F	11	25	5	4
S7	Th9/A	27/M	13	31	3	2
S8	Th8/A	41/F	9	34	5	5
S9	Th11/A	39/F	10	24	5	3
Group mean		34.8	9.8	39.7	4.5	3.6
SD		6.3	5.1	26.6	3.6	1.7

1ASIA impairment scale: A: no sensory or motor function is preserved; B: sensory is preserved below the level, but not motor. 2M: male; F:female; 3 MI assessed with Vividness of Motor Imagery Questionnaire (VQIM), range 1-5 (1: high, 5: low imagination), 4Ability of attempt to move the right foot with intensity of the feeling (1: very weak; 6: very high) and frequency of spontaneous attempt in daily life (1: very rare;6:very often

The measures were performed at the outpatient clinic and were repeated within 6 months to assure the completeness of SCI. Only one subject (S4) reported some clinical sensation (light touch) at the sacral dermatomes but had complete paralysis of the lower limbs and the SSEP and MEP were completely abolished. Twelve age-matched healthy right-handed volunteers (5 females, 7 males, mean age 29 years, SD 3.7) were recruited as controls.

None of the participants had suffered a brain lesion or had a history of neurological or psychiatric illness. Informed consent was obtained from all subjects and they were reimbursed for their participation in the study. The experimental protocol was approved by the Ethics Committee of the Balgrist University Hospital of Zurich, Switzerland

3.2.3.2. Assessment of movement attempt and execution

The motor task studied in the fMRI experiments consisted of repetitive alternating dorsal and plantar flexion of the right foot (30°-0°-45°) at a self-paced rhythm of approximate of 0.5 Hz. The ability to attempt moving the foot (motor attempt, MA) was assessed as follows. The perceived intensity and frequency of attempted movements was rated in a structured interview on phantom sensations, which had been developed for evaluating phantom body phenomena, paresthesia and movement sensations in SCI patients. Of particular relevance was rating the intensity of the feeling to move the right foot and the frequency of spontaneous attempts in daily life. Answers were noted as qualitative descriptors and both the phenomena's frequency and intensity were individually rated using a 6-point scale (see Table 1). The verbal instruction for MA in SCI patients was: "Try to move your right foot up and down at an approximate speed of 0.5 Hz". Correct performance was controlled using an adapted version of the controllability of motor imagery (CMI) described by (Naito et al., 2002). With eyes closed, the subjects were required to try moving their right foot as described above and, on command, to promptly give a verbal description of the foot position (flexed or extended). In healthy volunteers attempt to move was not required as the MA task is difficult to perform without generating isometric muscle contractions. Instead, they had to execute the foot movement (motor execution, ME). Following instruction, the ability of the controls to move their right foot up and down was visually verified.

3.2.3.3. Assessment of motor imagery

The ability of the subjects to perform MI was assessed with the Vividness of Motor Imagery Questionnaire (VMIQ, Isaac et al., 1986). To achieve consistent performance of MI in both groups and avoid muscle activity in the healthy subjects, all were trained with eyes closed to mentally move their right foot (dorsal and plantar flexion) outside of the scanner. To control for proper task performance, the CMI was applied here as in the MA task (see above, Naito et al., 2002). The training was continued up to the point where subjects could fulfill the requirements of the CMI and felt comfortable with the task.

3.2.3.4. Experimental protocol

Brain activation patterns underlying execution and imagination of foot movements were investigated with fMRI. Experimental conditions were presented within a fixed-order sequence consisting of movement attempt (execution in the controls) followed by imagination. Each experimental condition was administered in a standard block design consisting of three 21-second periods of baseline alternating with three 21-second periods of motor task. For the ME / MA condition the baseline was rest, for the MI condition the baseline condition consisted of silent automatic upwards counting starting from number six. This rest condition was chosen to make a clear distinction between the mental motor task and the rest condition (i.e. to ensure the subjects stopped imagery). Starting with six avoids the tendency of subjects to imagine counting with their fingers. All execution and imagery tasks were self-paced at a rate of approximately 0.5 Hz. The beginning and end of each activation period was signaled with verbal commands “go” and “stop” for ME and MA and “go” and “six” for MI, transmitted over the MR scanner’s intercom system. Correct task performance during data acquisition was visually controlled. This allowed monitoring of any movements or apparent change in the resting state of the non-moving limbs by the examiner. Overt motions were visually controlled and never observed during the MI task in healthy controls.

3.2.3.5. Scanning procedure

Blood oxygenation level dependent (BOLD) sensitive fMRI was carried on a 1.5 T whole body scanner equipped with a standard 6-channel head coil. T1-weighted whole-brain

anatomical reference volume data with an isotropic spatial resolution of 1.2 mm were acquired with a 3D spoiled, gradient-echo sequence [TE (echo time)= 9ms, TR (repetition time) = 50ms]. FMRI was conducted using a single-shot, gradient-echo, echo-planar imaging (EPI) sequence (TE = 55ms TR = 3000ms, flip angle 90°). For each task 126 time points were acquired consisting of 30 contiguous, axial slices (resolution 5 x 3.4 x 3.4mm) covering the entire brain.

3.2.3.6. Imaging analysis

Image analysis was performed using SPM99 (Welcome Department of Cognitive Neurology, London) under MATLAB 6.1 (Mathworks Inc., Natiek, MA, USA). The first two volumes of each fMRI time-series were discarded. For each subject, all remaining EPI volumes were realigned to the tenth volume of the first time series. A mean image was created and the anatomical image was co-registered with this mean image. After co-registration, the structural image was spatially normalized into the reference system of a representative brain template (Montreal Neurological Institute, MNI) using an affine and nonlinear transformation. The normalization parameters were subsequently applied to the functional images. Finally, the EPI images were re-sampled to a voxel size of 3x3x3 mm and smoothed with a Gaussian kernel of 10 mm full-width-at-half maximum (FWHM). The statistical analysis was performed at two levels in the context of the General Linear Model. Each single condition was modeled using a delayed boxcar function convolved with the hemodynamic response function. This data analysis was performed on a subject by subject basis to identify the general network involved in the respective task by comparing the activation with the rest condition.

Group analyses were performed according to the random effects procedure, using the single subject contrast images as input (Friston et al., 1996). Four group-wise parametric maps were generated using a one-sample t-test as ME and MI of foot movements in healthy subjects and MA and MI of foot in the SCI patients. Additionally for the second level analysis four contrasts were defined: *(i)* MA in SCI patients compared with ME in healthy controls; *(ii)* MI in SCI compared with MI in healthy controls; *(iii)* ME compared with MI in healthy controls; and *(iv)*. MA compared with MI in SCI patients.

For analyzing the results a region of interest (ROI) approach was used. Based on the known functional neuroanatomy of the human sensorimotor system (Jackson *et al.*, 2001; Lafleur *et*

al., 2002), the following ROIs were defined for both hemispheres: precentral and postcentral gyrus, paracentral lobule, supplementary motor area (SMA), cingulate motor area (CMA), frontal operculum, superior and inferior parietal regions, thalamus, basal ganglia and cerebellum. The anatomical ROIs were defined according to an automated anatomic atlas (Tzourio-Mazoyer *et al.,* 2002). For each activated cluster, the volume of activation and the maximal signal intensity were determined and the activation in MNI coordinates obtained using the "WFU-Pickatlas" a web-based interactive program, which returns the coordinates of a specified ROI with the implementation of a small volume correction (SVC, (Maldjian *et al.,* 2003). The chosen threshold was set at $p<0.01$ because of the relatively weak activation expected for foot movements as already described in other fMRI investigations (Dobkin *et al.,* 2004; MacIntosh *et al.,* 2004).

3.2.4.Results

3.2.4.1. Behavioral Data

In the structured interview all SCI subjects claimed to be able to attempt moving their foot and to differentiate between attempted and internally simulated movements. The ability to perform both tasks was further confirmed by the test for controllability of motor imagery (CMI, Naito et al., 2002) since all subjects were able to indicate the posture of their foot during both tasks. The patients were able to rate the intensity of their feeling during attempted movements on the 6-point scale, as well as the frequency of spontaneous daily performance (Table 1). The intensity was described as medium to very high during task performance (mean 4.5, SD 3.6, range from 3 to 6). In contrast, the daily performance was lower (mean 3.6, SD 1.7, range from 3 to 6). The intensity and frequency of task performance were significantly correlated ($r = 0.77$, $p<0.05$). In the vividness of motor imagery questionnaire (VMIQ) the performance of the SCI patients did not significantly differ from that of the healthy controls (mean 39.7, SD 26.6 and 44.3, SD 16.3 respectively).

3.2.4.2. FMRI study

1. Motor execution (ME) in healthy controls and movement attempt (MA) in SCI patients

In the controls, dorsal and plantar flexion of the right foot activated the left primary sensorimotor cortex (M1/S1) and bilaterally mesial (SMA, pre-SMA, CMA, CMAr), dorsal premotor (PMd) and ventral premotor (PMv) areas. Further, left-sided activation was observed in the superior (SP) and inferior (IP) parietal lobules, in thalamus, posterior putamen, and in anterior cerebellum (Table 2, Fig. 1).

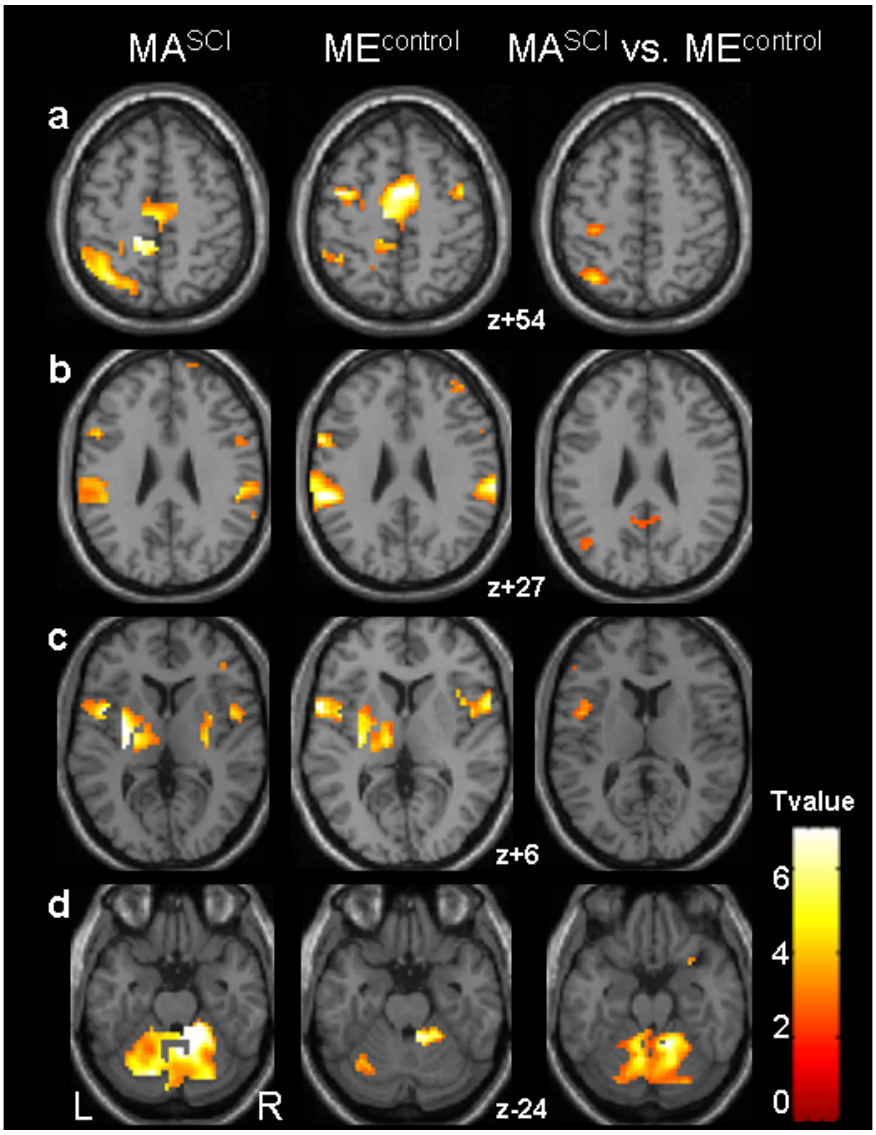
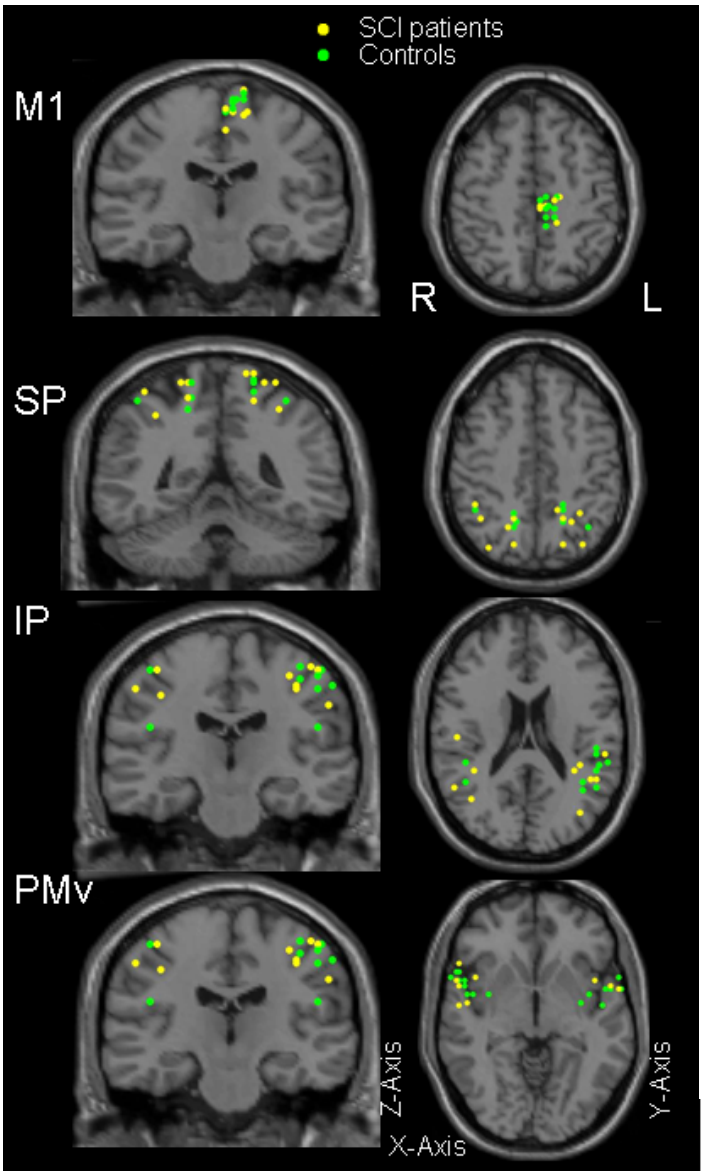


Figure 1: Activation patterns (group analysis) in SCI patients and controls displayed on mean anatomic T1-weighted images. *Left row:* Movement attempt (MA) in SCI patients. *Middle row:* Movement execution (ME) in controls. *Right row:* Movement attempt (MA) in SCI patients contrasted to movement execution (ME) in controls. *a:* central region, superior and inferior parietal areas (SP and IP); *b:* IP area, premotor ventral (PMv) and prefrontal cortex (PF); *c:* premotor ventral (PMv), putamen/pallidum, thalamus; *d:* cerebellum. Coordinates of significant regions in Tables 2 and 4.

When the SCI patients attempted to move their foot the pattern of activated regions was very similar to that found in the controls during execution. In addition, new significant clusters were found bilaterally in the prefrontal (PF) and SP cortex, in the right PMv region and the posterior putamen (Table 2).



The single subject analysis revealed activation in the primary motor cortex in all 9 SCI patients (Table 3). In this analysis, a considerable variation in volumes and t-values was found in the primary motor and somatosensory (S1) foot representations of the SCI patients during MA. Figure 2 displays for the individual subjects the activation maxima in the foot motor region. The greater scatter of the individual SCI data is most probably responsible for the smaller activation extent and intensity found in the group analysis for the patients during MA compared to ME in healthy subjects. Figure 2 also displays the activation maxima of each subject in PMv, SP, and IP

Figure 2: Displayed are the local maxima of the single subject activations for movement attempt in SCI patients and execution in controls after normalization for primary motor cortex (M1), superior parietal cortex (SP), inferior parietal cortex (IP), premotor ventral (PMv). *Yellow:* SCI patients. *Green*: controls. *Left row:* x, y coordinates projected onto a transverse section of a representative MNI standard brain through the most inferior local maxima. *Right row:* x, z coordinates projected onto a coronal section through the most anterior local maxima. Note that the general scatter is due to the fact that several higher and lower sections have been projected onto this one.

Table 2. MNI coordinates of significant cluster maxima, t-values, and volumes in the group analyses for executed, attempted, and imagined movements versus baseline in healthy controls and SCI patients (threshold p<0.01, corrected)

	movement execution healthy			movement attempt SCI			motor imagery healthy			motor imagery SCI		
functional ROI	x y z	max. t value	volume (voxel)	x y z	max. t value	volume (voxel)	x y z	max. t value	volume (voxel)	x y z	max. t value	volume (voxel)
M1	-6 -36 60	11.51	266	-12 -33 60	9.75	95						
S1	-15 -39 75	5.55	26	-30 -45 66	3.26	8						
S2	-57 -21 18	4.77	42	-60 -21 15	9.75	35				-63 -21 30	4.05	9
SMA	-9 -18 57	7.91	300	3 -21 57	6.88	124	-18 -6 66	3.08	5			
pre-SMA	0 0 48	10.62	241				6 6 51	4.19	40	-9 18 45	3.26	14
CMA	-6 -30 48	5.22	29	-12 -36 54	8.74	77						
				-3 -3 42	5.47	105						
CMAr	0 0 45	12.18	229				6 9 39	3.55	21	-6 0 36	6.63	47
PMd	45 -3 48	7.68	51									
	-36 -3 57	7.98	72				-36 -6 54	3.31	8			
PMv				54 6 30	4.42	28	51 12 39	3.85	9	54 12 27	5.04	48
	-57 6 24	8.11	115				-33 -3 39	3.37	5			
IFG po	60 9 9	8.92	97	45 9 12	3.36	13	60 15 -3	3.87	13			
	-57 6 6	8.85	110	-45 6 6	7.13	148	-48 3 0	5.01	35	-42 9 6	9.60	117
SP				15 -63 66	5.26	37						
	-27 -48 69	5.39	69	-30 -63 57	7.55	165				-30 -51 69	4.66	5
IP	66 -27 30	7.03	170	54 -30 24	6.56	111	54 -30 24	3.94	18	66 -33 33	6.65	216
	-54 -36 27	9.28	239	-57 -39 39	5.15	319	-60 -33 24	3.34	7	-54 -48 30	10.47	527
PF				42 39 3	3.8	20	30 33 -15	5.12	11	54 42 0	8.40	148
				-51 15 30	4.14	8	-45 15 -6	5.69	235	-54 30 9	6.73	471
TH										24 0 3	3.96	48
	-9 -18 -3	8.80	106	-21 -15 6	5.81	101				-21 -12 3	3.37	13
LN				30 -15 6	4.56	77				-30 9 3	7.85	18
	-30 -15 6	6.46	87	-30 -21 3	9.66	129	-24 -6 -6	8.09	17	-21 -3 0	4.33	51
CB	27 -42 -27	7.26	99	9 -45 -18	20.86	553						
	-33 -57 -30	6.41	44	-18 -72 -24	7	146						
				27 -4 5 -45	7.71	10						
	-30 -54 -45	4.81	14	-9 -84 -27	6.11	7						

ROI, region of interest; M1, primary motor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SMA, supplementary motor area; CMA, cingulate motor area; PMd, premotor dorsal cortex; PMv premotor ventral cortex; IFGpo, inferior frontal gyrus pars opercularis; SP, superior parietal cortex; IP, inferior parietal cortex; PF, prefrontal cortex; TH, thalamus; LN, lentiform nucleus; CB, cerebellum.

2. Motor imagery (MI) in healthy controls and SCI patients

During imagined movements the healthy subjects activated the left PMd, the mesial PM areas, and the PMv cortex bilaterally. Significant bilateral clusters were also found in the PF

and IP cortex and a contralateral one in the anterior putamen (Fig. 3, Table 2). BOLD signal changes in the left primary motor and S1 cortex was significant in only 3 of the 12 subjects (Table 3) and did not reach significance in the group.

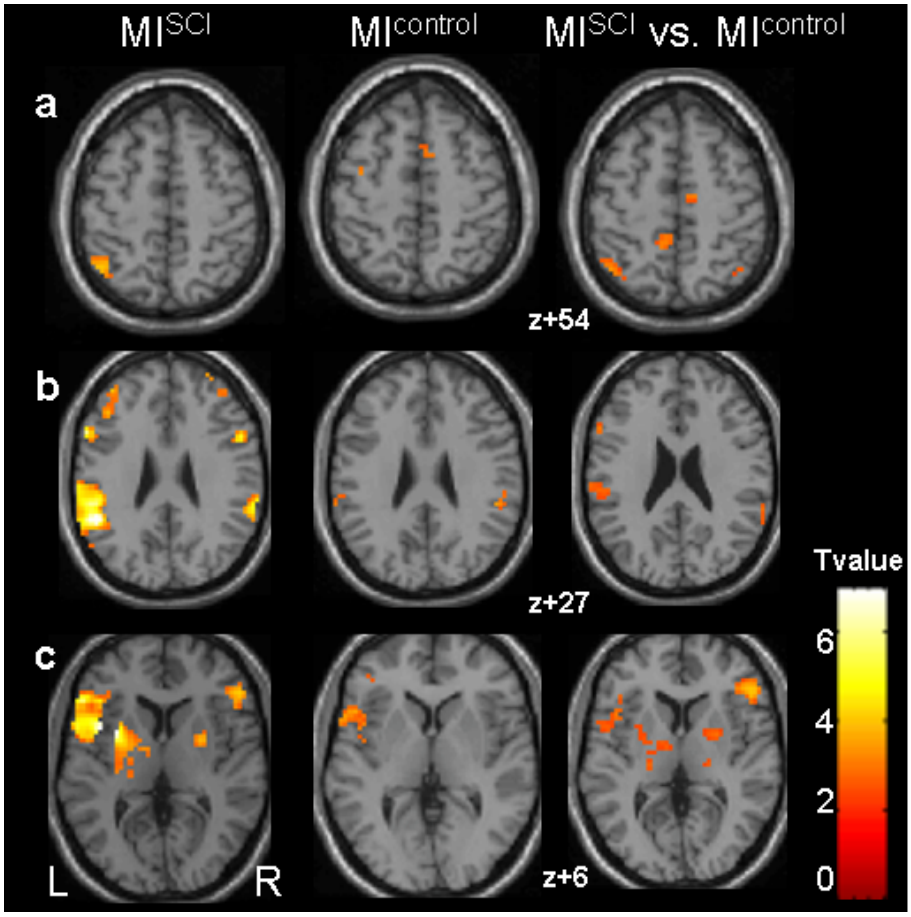


Figure 3: Activation patterns (group analysis) in SCI patients and controls displayed on mean anatomic T1-weighted images. *Left row:* motor imagery (MISCI) in SCI patients. *Middle row:* motor imagery (MIcontrol) in controls. *Right row:* motor imagery (MISCI) in SCI patients contrasted to motor imagery (MIcontrol) in controls. *a:* central region, superior and inferior parietal areas (SP and IP); *b:* IP area, premotor ventral (PMv) and prefrontal cortex (PF); *c:* premotor ventral (PMv), putamen/pallidum, thalamus. Coordinates of significant regions listed in Tables 2 and 4.

The main findings in SCI patients during MI were large activated clusters in IP and PF cortex, as well as in thalamus, anterior putamen and pallidum bilaterally (Table 2). Other activated areas included the mesial and ventral PM cortex, similar to the control group. The majority of the subjects (7 out of 9) however, had activation in the primary motor cortex (Table 3).

Table 3. Frequency of single subject activation in specified ROIs

functional ROI	execution controls N=10	movement attempt SCI N=9	motor imagery controls N=10	motor imagery SCI N=9
M1	10 / -	9 / -	3./ -	7 / -
S1	10 / 5	6 / 4	3 / -	3 / 1
S2	9 / 5	6 / 4	3 / 3	5 / 3
SMA	10	7	5	8
CMA	10	7	5	7
PMd	8 / 7	5 / 4	5 / 2	3 / 2
PMv	8 / 7	5 / 4	5 / 5	5 / 7
IFGpo	6 / 3	3 / 5	5 / 3	5 / 4
SP	9 / 5	9 / 7	7 / 1	4 / 3
IP	6 / 4	6 / 4	7 / 6	9 / 9
LN	4 / 0	3 / 2	-/-	-/-
CB	9 / 4	8 / 7	4 / 3	3 / 3

Number contralateral / Number ipsilateral. Abbreviations: see Table 2

3. Contrast between movement attempt (MA) in SCI and execution (ME) in healthy

The contrast between MA in SCI patients and ME in healthy volunteers revealed an overlap of many regions activated in both groups. However, MA produced more activation than ME in several regions: left PMv and putamen resp. pallidum, and bilaterally in SP and IP lobules, PF cortex and cerebellum (Table 4, Fig. 1). In contrast, no significant differences were found when ME in healthy controls were compared to MA in the SCI patients.

In the single subject analysis, although considerable variation in extent and intensity was found in the primary motor and S1 foot representations of the SCI patients for MA, the differences with the ME values in healthy subjects did not reach the significance level (t-test, resp. F-test for the standard deviations).

4. Contrast between MI in SCI patients and in healthy controls

To find out whether MI in paraplegia activates the same regions as MI in healthy controls and to the same degree, a contrast between patients and controls was performed. This contrast mainly revealed the presence of bilaterally activated clusters in the IP and PF cortex of the SCI patients (Table 4, Fig. 3). Activation was greater in the SCI patients in all regions activated by MI, except for SP and secondary somatosensory (S2) cortex (Table 4). Bilateral stronger activation was also disclosed in the thalamus and putamen/pallidum. The opposite

contrast, i.e. between MI in healthy and MI in SCI, did not disclose any increased or additional activation.

Table 4. Coordinates of significant cluster maxima, t-values, and volumes for the contrasts in healthy controls and SCI patients (threshold p<0.01, corrected)

	Controls ME vs MI					SCI MA vs MI					SCI MA vs ME controls					SCI MI vs controls MI					SCI MI vs ME controls				
functional ROI	x	y	z	max. t value	volume (voxel)	x	y	z	max. t value	volume (voxel)	x	y	z	max. t value	volume (voxel)	x	y	z	max. t value	volume (voxel)	x	y	z	max. t value	volume (voxel)
M1	-3	-36	60	10.87	262	-12	-33	60	7.34	111															
S1	18	-45	75	5.07	40																				
	-15	-39	75	6.05	29																				
SMA	9	-15	66	10.97	501	6	-24	57	5. 94	45						12	-12	54	3.26	5					
CMA	-3	-36	51	6.00	53	-12	-36	54	6.63	70															
CMAr	-3	0	39	11.82	169											-6	0	39	3.26	12					
PMd	15	-21	66	5.56	12																				
	-15	-15	69	3.63	13																				
PMv						51	12	27	5.24	37						54	12	30	2.91	8					
IFGpo	42	9	6	3.28	8																				
											-42	9	12	3.46	40	-45	12	6	2.99	22					
SP						15	-72	51	3.99	24	30	-60	63	3.75	12										
	-18	-42	63	5.46	41						-30	-63	57	4.92	62						-36	-66	51	3.43	6
IP	63	-24	18	7.98	152	42	-63	27	4.86	88	39	-72	36	3.41	30	63	-45	33	3.67	91	51	-63	36	3.59	86
	-51	-27	18	8.14	100						-36	-63	54	4.13	17	-60	-51	33	3.53	109	-54	-48	36	4.29	285
	45	-42	54	3.64	23	42	-48	45	4.38	23															
	-39	-51	60	6.1	5						-42	-72	36	3.37	42	-42	-60	54	3.44	30					
PF						42	42	18	5.88	112	30	12	-21	3.84	6	51	30	6	4.08	152	27	66	18	4.68	25
																-36	33	39	3.80	41	-42	30	30	4.63	466
											-30	45	-15	3.97	39	33	21	36	3.13	11	57	30	15	4.51	120
																-45	18	3	3.27	15	-54	15	24	2.72	5
TH																21	-21	9	3.02	7					
	-21	-24	6	3.83	14	-21	-24	-3	4.94	21						-9	-6	9	3.1	18					
LN																21	-3	-6	3.3	81					
	-30	-12	6	5.03	46	-27	-15	6	6.85	48	-30	-6	-6	3.47	29	-27	6	3	3.14	53					
CB	15	-42	-24	8.22	81	9	-45	-21	6.21	96	12	-48	21	7.92	384	21	-45	-27	3.01	9					
	-36	-57	-39	7.09	98	-15	-48	-15	4.27	24	-9	-63	-24	6.34	314										
	27	-69	-27	4.21	17						27	-45	-45	4.36	14	9	-57	-15	3.01	11					
	-24	-36	-30	3.73	10	-12	-84	-27	3.86	43	-30	-81	33	4.43	43										

Abbreviations: see Table 2.

6. Correlation of behavioural data and fMRI data

For the SCI patients correlation coefficients were computed between the quantitative aspects of the BOLD signal in all ROI's (max t-values and volumes of activation) and the clinical and behavioral data of the individual subjects (number of disconnected segments, time since injury, VMIQ scores, intensity and frequency in the 6-point rating scale for MA). No correlation coefficient reached the significance level, neither for MA nor for MI.

3.2.5. Discussion

The present study assessed the ability of chronic SCI patients to internally distinguish between attempted and imagined movements of their paralyzed feet and how these differ from executed and simulated movements in healthy controls. Four main findings summarize our results. First, the behavioural data clearly demonstrate that chronic complete SCI patients retain their ability to subjectively differentiate between the executive features required for MA and the cognitive ones necessary for MI. Secondly, this behavioural finding was confirmed by fMRI data revealing distinctly differential patterns of activation for the two conditions. Moreover, when SCI patients attempted to move their paralyzed foot the same network was recruited as when healthy subjects actually executed the foot movement. The same was true for the internal simulation of the movements, which activated the regions previously described for MI in healthy subjects and also seen in the controls of the present study. Third, our study confirms that during MA cortical motor areas, in particular the primary sensorimotor cortex, are functionality preserved in SCI patients, though with reduced activation due to a long period of disconnection. Finally, the enhanced activation in most secondary motor areas and the additional recruitment of prefrontal and parietal areas both during MA and MI in SCI patients suggests that the paraplegic condition may require an increase in attention allocation to perform the tasks and/or have induced some adaptive changes in the functional networks involved.

3.2.5.1. Movement attempt in SCI patients

Few neuroimaging studies have addressed MA in chronic spinal cord injured patients (Sabbah et al., 2002; Cramer et al., 2005; Halder et al., 2006; Fallani et al., 2007). The most

recent fMRI investigation (Cramer et al., 2005) reported an activation pattern during MA similar to that observed during execution in healthy controls, though with decreased volumes in most cortical regions examined. The present study replicated this activation pattern however, with the exception of the primary motor cortex, equivalent or greater BOLD activation was found in all other areas, as well as recruitment of several additional regions (PMv, SP, IP, and PF cortex). In addition, in the present investigation the basal ganglia were always activated, in the healthy subjects as well as in the chronic SCI patients. This is in contrast with Cramer et al. (2005) who reported a significant BOLD signal in the pallidum only for their SCI population and who interpreted this finding as the emergence of pathological activation. Differences in experimental designs most likely account for the discrepancy between these findings. In the study by Cramer et al. (2005) attempted movement was initiated by a video of the target motion shown before and during the fMRI session, and the foot task used in their investigation, an attempt to crush a displayed object every 3 s, was more complex than our self initiated, simple, repetitive dorsal and plantar foot flexion. Furthermore, healthy subjects in their study performed also a movement attempt task, which is difficult to perform without isometric muscle contractions, as opposed to the simple motor execution used in our study.

The fact that no significant differences in BOLD signal between MA in the SCI patients and ME in healthy controls were found in primary sensorimotor and PM mesial cortex, supports our assumption that these are two corresponding conditions, which can be contrasted with each other, despite the fact that attempt to move can only be indirectly controlled through behavioural tests, as the movements are not visible. The similarity between the network activated in SCI patients during MA and the execution network of healthy subjects additionally provides the neural and thus “visible” evidence for task performance. In fact, this finding in chronic paraplegics, who were all neurophysiologically tested for completeness of the disconnection, reveals their retained potential to initiate and control foot movements, even after a long period of non-use, as suggested by the behavioural assessment.

Consistent with results of earlier investigations (Lacourse et al., 1999; Halder et al., 2006) in the group analysis the activation in the primary motor cortex during MA was reduced as compared to ME of healthy controls, but this did not reach the significance level. At the single subject level however, the size and intensity of signal changes in the primary motor cortex did not differ significantly when controls and patients were compared, suggesting that

the smaller cluster observed in the SCI patients at group level was probably due to the scatter of the individual data during the averaging process. In spite of the electrophysiological assessed interruption of the sensory afferent pathway from the periphery, a small BOLD signal has been observed in the postcentral region confirming our earlier findings of a primary somatosensory (S1) foot representation recruitment in complete SCI patients (Alkadhi et al., 2005). This postcentral activation can be attributed to an efference copy of the ongoing movement in sensory regions (Holst and Mittelstaedt, 1950) A recent fMRI investigation with ischemic nerve block on the lower limb also disclosed activation in S1 giving further support to this hypothesis (Christensen et al., 2007).

Two present findings suggest that MA is a more demanding task than ME. First, both the additionally activated focus in the PF cortex and the activation enhancement in the parietal lobe suggest the existence of a stronger cognitive component during MA. This may reflect the intense attention allocation required from the chronic SCI patients to perform a considered easy over-learned task (Allen et al., 1997; Rowe et al., 2002; Rushworth et al., 2003). Second, the comparison between attempted and performed foot task revealed stronger activity specific for MA in the parietal cortex, in cerebellar regions, and in the putamen. One cannot exclude that the chronic paraplegic condition has also induced adaptive changes in these key structures yielding sensorimotor transformations and movement guidance (Catalan et al., 1998; Allen et al., 2005). The scattered activation seen in the individual activation in the SCI individual data in parietal and premotor regions also points to the presence of adaptive changes. Recent EEG data strongly suggest modifications in connectivity between cortical regions during MA in SCI patients compared to healthy subjects (Fallani et al., 2007).

3.2.5.2. Motor imagery in SCI patients

In our earlier study (Alkadhi et al., 2005), SCI patients were asked to mentally move their right foot. This instruction led to enhanced activation of an extensive network of brain areas comprising regions activated both during motor imagery and during execution in healthy controls (Lafleur et al., 2002). In the present investigation, MI in SCI patients recruited areas that were spatially more restricted to frontal, mesial and premotor ventral cortex, parietal regions, thalamus and striatum. These are regions that normally activate during MI in

healthy subjects (Gerardin et al., 2000). Compared to our former study where the primary motor cortex was significantly activated during MI, activation in the present study was inconsistently observed in the individual subjects, in accordance with previous investigations using similar tasks (Porro et al., 1996; Gerardin et al., 2000;). In contrast, during MA the primary motor cortex was consistently activated, though at a reduced intensity. These fMRI findings clearly confirmed the results in the behavioral assessments namely that the SCI patients were performing distinct MA and MI tasks.

Prefrontal and parietal areas showed enhanced activation during MI in the SCI patients when compared to the control group. This increased activity confirms our previous findings (Alkadhi et al., 2005), but is not in line with those of Cramer and colleagues (2005) who, in a similar contrast, did not observe significant changes in these regions. In their study, the only cortical area showing increased activation during MI was the superior temporal gyrus, a region important for the visual perception of biological motion, which never activated in our investigation. These conflicting findings between the two studies can be attributed to differences in the experimental protocols used. Videos of the required complex movement were shown in their study with the instruction to imagine movement completion, which may have induced unconscious strategies leading to 3rd person motor imagery. As recently demonstrated, kinesthetic (1st person) and visual (3rd person) motor imagery are supported by different neural networks (Solodkin et al., 2004). In our experiment no visual stimuli were presented and the subjects with eyes closed were specifically instructed and trained to prevent developing a strategy leading to visualization of their limb. Accordingly, activation in visual regions was not observed during attempted or imagined movements.

3.2.5.3. Central motor control in paraplegia

The present investigation indicates that in chronic paraplegic patients the central programs for execution of foot movements and their internal simulation remain preserved, activating several common regions and, in addition, other distinct ones specific to either task. MA and MI in a status of chronic deafferentation and deefferentation are complex tasks, which recruit cortical regions involved in higher cognitive processes. Despite every effort in this study to distinguish between the two tasks, taking into consideration the single subjects' activations, as well as their contrasts, we cannot completely rule out the likelihood of a contamination of

either task by the other. This possibility may explain activation of the PF cortex during MA and of the primary sensorimotor cortex during MI observed in a few subjects.

How the control of virtual foot movements can be preserved after a prolonged period of complete disconnection? In patients with chronic hemiplegia the ability to construct internal action representations of the upper limbs can be robust even after years of limb non-use (Johnson-Frey, 2004). The process of matching the final position of one's limbs with an intended movement is achieved through a comparison process between the predicted sensory consequences of the action and the actual sensory feedback (Desmurget and Grafton, 2000; Wolpert and Ghahramani, 2000). Since peripheral cutaneous and proprioceptive afferents of the lower limbs are unavailable in complete SCI patients, this process can be accomplished solely by means of stored motor programs and the resulting stream of motor commands with their sensory signals generated through corollary discharge (Blakemore and Sirigu, 2003). The additional fact that the SCI patients have continuous daily visual control of their body may also play a role in maintaining an internal representation of their limbs through a continuous updating by simply looking at them (Wolpert et al., 1998). These speculations are supported by the retained integrity of the internal action representation in our patients as revealed by both the structured interview and the fMRI data.

It has been suggested that parietal areas constitute the neural substrate for the storage of visual and kinaesthetic limb postures, which are subsequently mapped onto corresponding motor regions (Sirigu et al., 1996). Damage to the parietal cortex leads to the inability both of maintaining an internal representation of the body (Wolpert et al., 1998) and of internal movement simulation (Sirigu et al., 1996). These findings indicate that the parietal cortex is a key structure in sensorimotor integration and, together with its interactions with the cerebellum, plays an important role in acquisition and recall of skilled movements (Allen et al., 1997; Shadmehr and Holcomb, 1997; Andersen and Buneo, 2003; Blakemore and Sirigu, 2003). The enhanced parietal and cerebellar activations observed in chronic SCI patients during MA and MI in our study suggests that some adaptive changes have occurred in these regions. The absence of sensory input may have modified the functionality of these areas in order to maintain an intact body representation and organize motor plans accordingly.

3.2.5.4. Clinical significance

The present study demonstrates in chronic paraplegics the retained functionality of neuronal networks that in healthy subjects are responsible for dorsal and plantar flexions of the foot and their internal simulation. This finding may have important clinical value when considering new treatment approaches aiming at functional recovery following spinal cord damage. If reconnection of the brain to the paralyzed limbs through the spinal cord is successful, according to our present data, the still functional motor programs should allow a certain degree of motor control. The apparent integrity of MI in SCI patients and the resemblance of their MA network with the ME network of healthy subjects suggest that the paraplegics still dispose of the full motor programs for overt and covert foot movements. Recent reports provide convincing evidence that mental practice based on motor imagery might be beneficial for learning new movements and/or strengthening memorized ones (Jackson et al., 2003; Lacourse et al., 2005; Cramer et al., 2007). We therefore suggest that MA and MI should be both beneficial in rehabilitative strategies after spinal cord injury for improving motor functions.

3.3. Study 3: Foot movement observation activates an internal representation in complete paraplegics

3.3.1.Abstract

Movement observation excites the motor representation used to execute the same movement in the premotor and parietal region the so called mirror system. The present study used functional magnetic resonance imaging to test this postulation in complete spinal cord injured (SCI) patients who are able to attempt to move their plegic foot. Twelve healthy subjects and nine SCI patients were scanned during execution of dorsal flexion and extension and the subsequent observation of video-clips showing the same movement. Performed and observed foot movements activated similar networks in the observation/execution matching system in the control group and the SCI patients although the patients showed plastic changes in several cortical areas of the mirror system. These results provide a reliable proof for the functionality of the execution network in SCI patients. The knowledge about the preservation of complex motor control systems might be very important when considering a restoration of spinal cord conductivity in complete SCI patients.

3.3.2. Introduction

The existence for an action observation/execution matching or mirror system was first discovered in the ventral premotor cortex of monkeys. Mirror neurons discharge both when the monkey performs a specific goal-related hand action and when it observes another individual performing the same action (Gallese et al., 1996; Rizzolatti and Craighero, 2004). In humans, evidence for this mechanism linking observation and action has been demonstrated in numerous neurophysiologic (Fadiga et al., 1995; Hari et al., 1998; Nishitani and Hari, 2000; Strafella and Paus, 2000) brain-imaging (Buccino et al., 2001, Grafton et al., 1996; Decety et al., 1997; Iacoboni et al., 1999; Grezes and Decety, 2002) and eye-tracking studies (Flanagan and Johansson, 2003). This system is distinct from the mirror neurons described in monkey premotor cortex since the induction arises from any kind of movement and is not restricted to goal-directed actions. The mirror system offers a possible explanation

of how we understand the actions of others: by directly mapping the visual representation of the observed action onto our motor representation of the same action (i.e. by “internally” executing them, Jeannerod, 1994; Rizzolatti et al., 2001; Rizzolatti and Craighero, 2004; Fogassi et al., 2005; Iacoboni et al., 2005). The observation of an action recruits a consistent network of cortical areas, including ventral premotor cortex (PMv), the parietal lobes and the superior temporal gyrus (STG, Fadiga et al., 2005). These brain regions form the core network of the mirror system involved in action encoding. Additional regions known for motor representation as primary sensorimotor cortex, pre-supplementary motor area, the basal ganglia and the cerebellum have also been involved in movement ovservation (Avikainen et al., 2002; Frey and Gerry, 2006; Hari et al.,1998; Grafton et al., 1996). These areas are sensitive to prior physical experience and are thought to store the motor vocabulary within (Calvo-Merino et al., 2005; Cross et al., 2006). For example, in the premotor cortex action observation is somatotopically represented (Buccino et al., 2001), similar to the gross-scaled somatotopy generally described in earlier neuroimaging studies for motor execution (Grafton et al. 1991; Rao et al. 1995). While the vast majority of animal and human studies report on upper limb movements, it could be also shown that observation of lower limbs activates dorsal regions of the precentral gyrus (Brodman area 6, Buccino et al., 2001), bilateral inferior parietal and ventral premotor areas of the motor network (Wheaton et al., 2004). Finally, Sakreida et al., (2005) reported that leg movement observation are stronger represented in the dorsal than ventral premotor cortex.

Patients with SCI provide a human model in which the effects of deafferentation and deefferentation on sensorimotor maps can be studied. While the reorganization of sensori-motor areas has been studied in various disorders of the brain and spinal cord during motor execution, there is still very limited knowledge in how far the cortical mirror system also possesses the capacity of neural plasticity. In this context we investigated the effects of complete spinal cord injury onto the organization of the observation/execution matching network. Foot movements are familiar to the SCI patients although they cannot longer physically perform them. Previous studies revealed the retained potential of chronic SCI patients to initiate movements of their dissconnected feet. Activation of the primary motor cortex during attempted foot movements has been reported in SCI patients using event-related potentials (Halder P et al., 2006; Lacourse MG et al., 1999) and fMRI (Sabbah et al., 2002); (Cramer SC et al., 2005). In these patients, cortical activation patterns involved in

motor control during attempted execution remained preserved although, reduced in almost all regions as compared to healthy subjects performing the same task (Sabbah P et al., 2002) (Cramer SC et al., 2005)

Cortical areas involved in the observation/execution system should be activated both during the execution and the observation of an identical movement as has been postulated by Rizolatti and his colleagues (2001). Based on this definition foot movement observation provides an external trigger, independent of body afferent inputs other than visual feedback, that should be able to induce an internal activation of the still intact motor control network in SCI patients. The main hypothesis of this work is that the observation/execution matching network (termed the mirror motor system) in complete SCI patients remains intact. This would provide additional evidence for the preservation of the complex motor control network in these patients and may supply useful clues for new rehabilitation approaches in paraplegic patients when physical performance is not adequately feasible.

3.3.3. Material and Methods

3.3.3.1. Participants

Nine paraplegic patients were recruited from the outpatient clinic (3 females, 6 males, and mean age 35 years, SD 6). The Edinburgh handedness inventory revealed clear right hand dominance for all subjects. For the nine patients the mean period following traumatic SCI was 9 years (range 2-20 years). All had clinically complete SCI between Th3 and L3, as assessed with the impairment scale of the American Spinal Injury Association (ASIA, Maynard et al., 1997), and confirmed by repeated electrophysiological recordings (motor evoked potentials (MEP) of the lower limbs and posterior tibial nerve somatosensory evoked potential (SSEP). Twelve age-matched healthy right-handed volunteers (5 females, 7 males, and mean age 29 years, SD 3.7) were recruited as controls. None of the participants had suffered a brain lesion or had a history of neurological or psychiatric illness. Subjects were reimbursed and informed consent was obtained after the nature and purpose of the study were explained. The experimental protocols were approved by the Ethics committee of the Balgrist University Hospital of Zurich, Switzerland.

3.3.3.2. Instruction and Assessment

The foot movement was a dorsal and plantar flexion performed at a self-paced rate of approximately 0.5 Hz. It was executed by healthy volunteers and attempted to move by the SCI patients. Prior to the scanning the task was task was practiced and controlled for correct performance. Instructions for control subjects and the patients were “Move your right foot up and down”. The experimenter visually controlled the performance in healthy subjects. In SCI patients an adapted version of the controllability of motor imagery (CMI, Naito et al., 2002) was used. With eyes closed, they were required to move their right foot as described above. On command, they had to stop the movement and give a verbal description of the foot position (flexed or extended). The training was continued up to the point where subjects could fulfill the CMI requirements and felt comfortable with the task. In addition, their perceived intensity and frequency of movement attempt was assessed using a structured interview on phantom sensations, which had been developed for evaluating static phenomena, paresthesias and movement sensations. Of special interest was the ability of attempt to move the right foot rated both with the intensity of the feeling and the frequency of spontaneous attempt in daily life. Answers were noted as qualitative descriptors and both the phenomena’s frequency and intensity were individually assessed using a 6-point rating scale.

3.3.3.3. Experimental protocol

The experimental conditions were presented within a fixed-order sequence consisting of execution of the self-paced foot movements (healthy subjects) or their attempt (SCI patients), followed by the observation of the same foot movement. Each experimental condition was administered in a standard block design consisting of three 21s periods of baseline alternating with three 21s periods of activation. For the execution and attempt condition the baseline was rest, and each activation period was signaled with the verbal commands “go” and “stop” transmitted over the machine’s intercom system. The foot movements had been previously videotaped showing a person’s right foot moving at rhythm of approximately 0.5 Hz. The baseline for the observation was a blank screen in the same color as the background during the observation video. The video sequences were back-projected onto a screen in the scanner room. Subjects viewed the stimulus display through a

mirror mounted on the head coil. They were instructed to maintain their gaze in the screen center.

3.3.3.4. Scanning procedure

Blood oxygenation level dependent (BOLD) fMRI was carried on a 1.5 Tesla whole body scanner equipped with a standard product transmit-receive head coil. T1-weighted whole-brain anatomical reference volume data with an isotropic spatial resolution of 1.2 mm were acquired with a 3D spoiled gradient echo sequence [TE (echo time)= 9ms, TR (repetition time) = 50ms]. FMRI data were obtained using a single-shot, gradient-echo, echo-planar imaging (EPI) sequence (TE = 55ms TR = 3000ms, flip angle 90°). For each of the 126 time points, 30 contiguous, axial slices (voxel size 3.4 x 3. 4 x 5mm) covering the entire brain were acquired.

3.3.3.5. Imagine analyses

Image analysis was performed using MATLAB 6.1 (Mathworks Inc., Natiek, MA, USA) and statistical parametric mapping (SPM99, Welcome Department of Cognitive Neurology, London). For each functional acquisition, data were realigned and normalized to the MNI template with a $3 \times 3 \times 3$ mm resolution. A 10-mm smoothing kernel was applied to the normalized images. For individual analysis, data from each run were modeled using the general linear model with separate functions modeling the hemodynamic response to each experimental epoch. Group activation maps were calculated by pooling the data for each condition across all subjects using a random effect analysis (Friston *et al., 1999*).

Performing an atlas-based region of interest (ROI) analysis the WFU-Pickatlas tool was used with the included anatomical automatic labelling (AAL) atlas (Tzourio-Mazoyer et al. 2002; Maldjian et al., 2003). Based on the known functional neuroanatomy of the human mirror system (REF Hamilton et al.), the following ROIs were defined for both hemispheres: precentral and postcentral gyrus, paracentral lobule, supplementary motor area (SMA), cingulate motor area (CMA), frontal operculum, superior and inferior parietal regions, thalamus, basal ganglia and cerebellum.

3.3.4. Results

3.3.4.1. Behavioral Data

In the structured interview all SCI subjects claimed to be able to attempt moving their foot. This was further confirmed by the test for controllability of motor imagery (CMI, Naito *et al.*, 2002) since all subjects were able to indicate the posture of their foot during both task. The patients were able to rate the intensity of their feeling during attempted movements on a six point rating scale, as well as the frequency of spontaneous daily performance. The intensity was described as medium to very high during task performance on the 6-point rating scale (mean 4.5, SD3.6) with a range from 3 to 6. In contrast, the daily performance was quite low (mean3.6, SD1.7). The intensity and frequency of task performance were significantly correlated ($r= 0.77$, $p<0.05$).

3.3.4.2. Execution of foot movement in healthy controls and attempt in SCI patients

In the structured interview all SCI subjects declared being able to attempt moving their foot. On a 6 point rating scale for the intensity of feeling the foot movement (1: very weak; 6: very high) scored a mean of 4.5 (SD 3.6, range 3-6) whereas, for the frequency of spontaneous attempt in daily life (1: very rare; 6: very often) a mean of 3.6 (SD1.7, range 1-6). The patients' ability was further confirmed by the test for controllability of motor imagery (CMI), (Naito E *et al.*, 2002) where all subjects correctly indicated the posture of their foot during prompt interruption of MA.

Group analysis in the controls during right foot movements revealed significant focal activations in the contralateral M1/S1 foot representation and in premotor cortical areas including bilateral mesial (SMA, pre-SMA, CMA, CMAr), ventral (PMv) and dorsal premotor (PMd) regions. Additionally, left-sided activation was observed in the superior (SP) and inferior (IP) parietal cortex, thalamus, posterior putamen, and bilaterally in the anterior cerebellum. When the SCI patients attempted to move their foot the pattern of activated regions was very similar to that found during EXE in the controls. In the group analysis, the primary sensorimotor activation had a smaller extent and less intensity, compared to those in healthy subjects. In addition, new significant clusters were found bilaterally in the prefrontal (PF) and SP cortex, and in the right PMv and posterior putamen.

The contrast between MA in SCI patients and EXE in healthy volunteers revealed that many similar regions were activated in both groups. However, MA elicited stronger activation than EXE in several regions: left PMv and anterior lentiform nucleus, and bilaterally in the parietal (SP and IP) and PF cortex as well as, the cerebellum. No significant differences were found when overt movements in healthy controls were compared to attempted ones in the SCI patients.

3.3.4.3. Observation of foot movement in healthy controls and SCI patients

In healthy controls observation of intransitive foot movements activated the core network of the execution/observation matching system including the right PMv cortex and bilaterally parietal regions and the superior temporal gyrus (STG). Posterior parts of the cerebellum and bilateral thalamus were also activated. The PMv activation was located in the inferior precentral gyrus at a slightly higher location than in the execution task at the border of PMd (z-level 36).

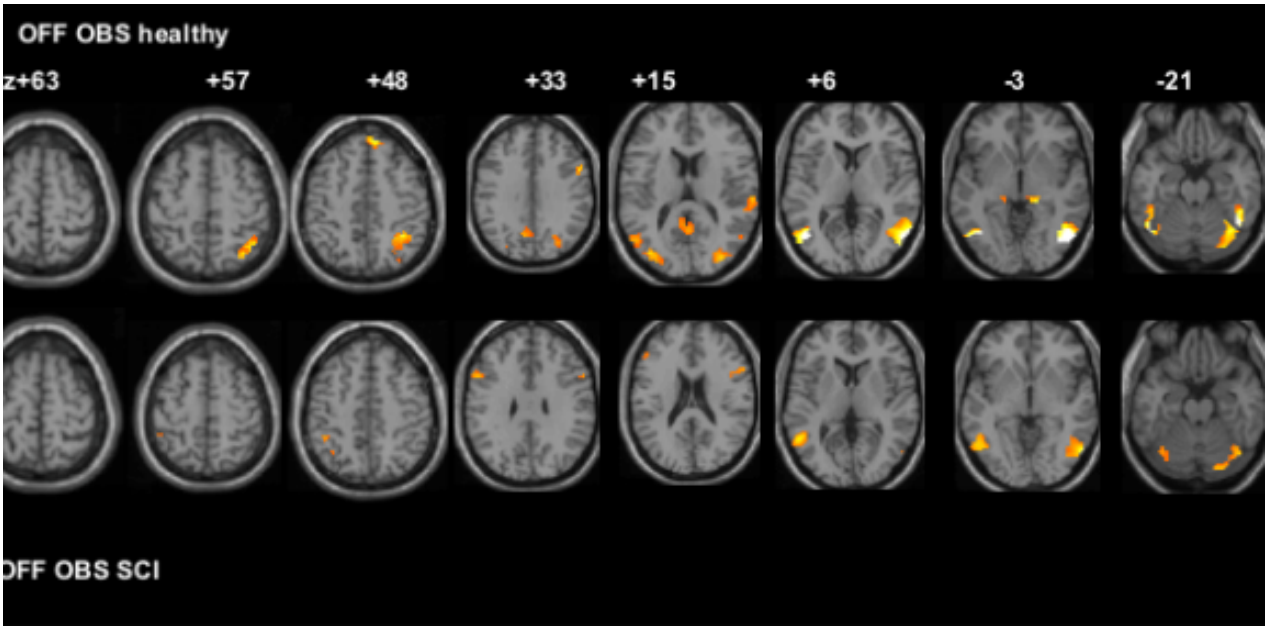


Figure 1 Activation patterns (group analysis) in healthy controls and SCI patients displayed on mean anatomic T1-weighted images. Upper row: Foot movement observation contrasted to baseline in healthy controls. Lower row: Foot movement observation contrasted to baseline in SCI patients. Significant regions listed in Tables 1 and 2.

The parietal activations were found in the intraparietal sulcus (IPS) extending to the adjoining SP and IP lobules. SCI patients, not physically able to perform the movement, had

a bilateral activation in PMv cortex while the inferior parietal lobule was activated only in the left hemisphere.

Table 1. MNI coordinates of significant cluster maxima, t-values, and volumes for execution and observation in healthy controls and SCI patients (threshold p<0.01, corrected)

	Foot EXE in controls			Foot OBS in controls			Attempt to move in SCI			Foot OBS in SCI		
Functional ROI	x y z	max. t value	volume (voxel)	x y z	max. t value	volume (voxel)	x y z	max. t value	volume (voxel)	x y z	max. t value	volume (voxel)
M1	-6 -36 60	11.51	266				-12 -33 60	9.75	97			
S1	-15-39 75	5.55	26				-30 -45 66	3.26	8			
S2	-57-21 18	4.77	42				-60 -21 15	9.75	35			
SMA	-9-18 57	7.91	300				3 -21 57	6.88	124			
pre SMA	0 0 48	10.62	241									
CMA	-6-30 48	5.22	29				-12 -36 54	8.74	77			
pre-CMA	0 0 45	12.18	229				-3 -3 42	5.47	105			
PMd	45 -3 48	7.68	51									
	-36 -3 57	7.98	72									
PMv				54 9 36	5.76	19	54 6 30	4.42	28	60 12 27	3.6	16
	-57 6 24	8.11	115							-54 12 33	4.84	19
IFG po	60 9 9	8.92	97				45 9 12	3.36	13			
	-57 6 6	8.85	110				-45 6 6	7.13	148			
SP				42 -57 57	4.46	30	15 -63 66	5.26	38			
	-27-48 69	5.39	69	-33 -66 57	4.83	13	-30 -63 57	7.55	180			
IP	66 -27 30	7.03	170	36 -48 48	6.31	60	54 -30 24	6.56	111			
	-54-36 27	9.28	239	-33 -78 39	3.41	8	-57 -39 39	5.15	319	-42 -42 48	3.74	18
TH				18 -30 -3	5.29	15						
	-9 -18 -3	8.80	106	-21 -30 0	3.89	7	-21 -15 6	5.81	101			
BG							30 -15 6	4.56	77			
	-30 -15 6	6.46	87				-30 -21 3	9.66	129			
CB	27 -4 -27	7.26	99	42 -57 -24	5.9	99	9 -45 -18	20.86	553	30 -81 -24	4.76	47
	-33 -57 -30	6.41	44	-48 -63 -21	6.53	38	-18 -72 -24	7	146	-36 -66 -21	3.77	30
							27 -4 5 -45	7.71	10			
	-30 -54 -45	4.81	14				-9 -84 -27	6.11	7			

ROI, region of interest; M1, primary motor cortex; S1, primary somatosensory; S2 secondary somatosensory area; SMA, supplementary motor; CMA, cingulated motor; PMd, premotor dorsa; PMv premotor ventral; IFGpo= inferior frontal gyrus pars opercularis, SP, superior parietal; IP, inferior parietal; A/SM, gyrus angularis and supramarginalis; PF, prefrontal; TH, thalamus; BG, Basal Ganglia; CB, cerebeLLUM

The main finding in the contrast between foot OBS in SCI patients and controls was the bilateral persisting activation of the mirror system in PMv, in the left SP and IP cortex, in the

basal ganglia and posterior cerebellum. The contrast revealed bilateral stronger activation in the PMv cortex and significant stronger foci in the the SP and IP region in the left hemisphere of the SCI patients. The SP cortex did not show any activation in the group analysis. However, in the single subject analysis, the SCI patients had a more frequent activation in the PMv, SP and IP cortex than the controls. The parietal clusters were quite scattered and therefore, did not reach a significance level in the group analyses. The inverse contrast revealed a small additional cluster in the lower PMv on the right side as well as, bilateral activation in CMA and posterior cerebellum.

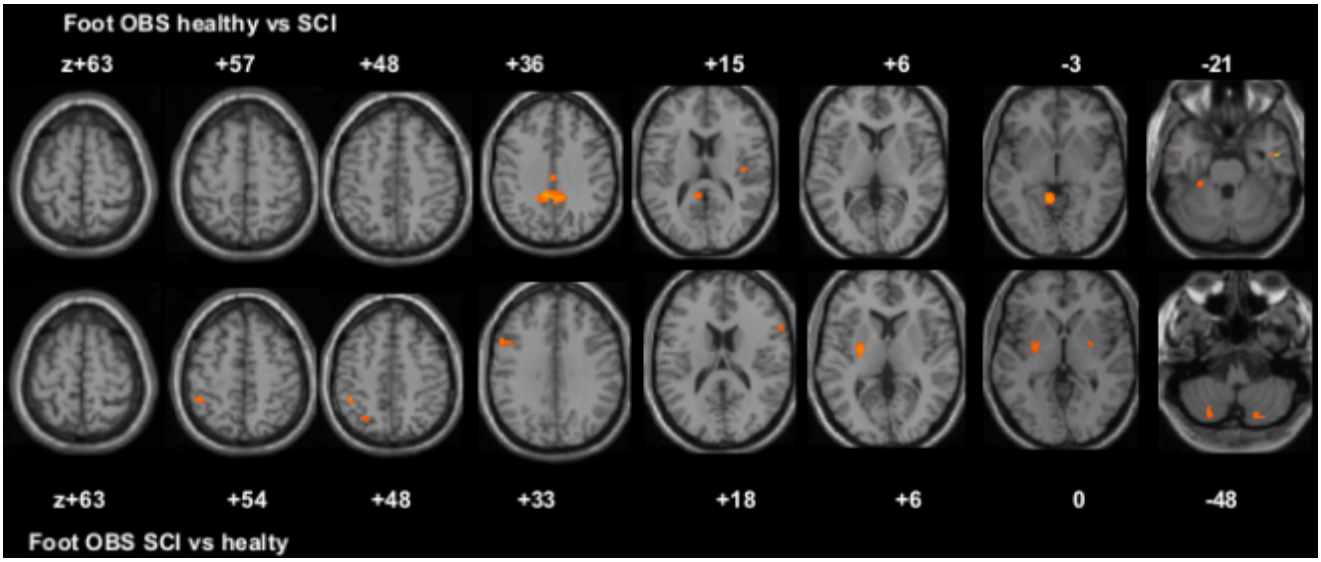


Figure 2 Activation patterns (group analysis) in healthy controls and SCI patients displayed on mean anatomic T1-weighted images. *Upper row:* Foot movement observation in. *Lower row:* Foot movement observation SCI patients vs. healthy Significant regions listed in Table 3.

Table 3. MNI coordinates of significant cluster maxima, t-values, and volumes in the group analyses for the contrast between movement attempt in SCI patients and execution in controls, and observation in SCI patients and execution in controls (threshold p<0.01, corrected)

Attempt to move	Foot OBS	Foot OBS

	in SCI vs EXE in controls			controls vs SCI			SCI vs controls		
Functional ROI	x y z	max. t value	volume (voxel)	x y z	max. t value	volume (voxel)	x y z	max. t value	volume (voxel)
CMA				-9 -42 39	4.09	224			
pre-CMA									
PMd									
PMv				39 -18 15	2.99	9	63 12 21	3.09	12
							-57 12 30	3.65	40
IFG po	-42 9 12	3.46	40						
SP	30 -60 63	3.75	12						
	-30 -63 57	4.92	62				-27 -66 48	2.85	7
IP	39 -72 36	3.41	30						
	-36 -63 54	4.13	17				-42 -42 48	3.43	25
	-42 -72 36	3.37	42						
BG							27 -6 0	2.62	5
	-30 -6 -6	3.47	29				-27 -9 6	3.31	42
CB	12 -48 -21	7.92	384	15 -33 -15	3.20	5	27 -72 -45	3.81	11
	-9 -63 -24	6.34	314	-12 -33 -12	4.25	21	-27 -72 -48	3.10	7
	27 -45 -45	4.36	14						
	-30 -81 -33	4.43	43						

Abbreviations see Table 1

3.3.5. Discussion

The results of this study confirm in chronic SCI patients the ability to attempt a foot movement as well as an intact mirror system for the integration of movement execution and observation. Although several changes induced by the spinal cord lesion can be found due to the lost ability to physically perform movements, the brain still can exploit the complex mechanisms of sensorimotor control. These findings are discussed in relation to cortical plasticity and potential application in SCI rehabilitation where mental training programs could be fruitful in a standard rehab protocol.

3.3.5.1. The observation/execution matching system

Movement observation and its execution are shown to have parallel effects on the mirror system (Rizzolatti et al., 2001). Therefore, the activation of the mirror system after exposure to foot movement observation implies an internal simulation of these movements in complete paraplegic patients. Our findings in the SCI patients are in line with a recent fMRI study addressing the observation/execution system in motor disorder (Burgmer et al., 2006). The patients suffered from a hemi paresis due to a conversion disorder, a psychiatric condition with a loss of bodily functions not caused by organic disorders. The investigation revealed similar brain activation patterns during attempted movements of the affected hand in patients and executed ones in the controls but no activation in the mirror system was found when the patients observed the same intransitive hand movements (Burgmer et al., 2006). The finding was interpreted as a disturbance of the representation of internal movement generation and represented a disturbance in the involuntary, preconscious levels of motor control (Burgmer et al., 2005).

The fact that in our study the complete paraplegic patients the execution/observation matching system was triggered by observation is another validation of the preserved internal movement representation for foot movements. This important result reveals for the first time an equivalent BOLD-signal for the retained integrity of a working–like representation of foot movements after a long period of nonuse. This finding complement the data obtained in the neuroimaging experiment for attempted execution and the behavioral assessments prior to the scanning session where the SCI patients indicated their ability to “execute” movements of their plegic feet.

Attempted execution in SCI patients revealed a similar activation pattern as the control group although with stronger signal in premotor and parietal cortex and in the cerebellum. These regions are reported to be especially involved in the control and performance of movements within the motor system (Allen G et al., 2005; Catalan MJ et al., 1998). The chronic paraplegic condition with its extinguished peripheral input and altered output mechanisms may have in addition induced adaptive changes within these brain regions.

Observation of this foot movement in healthy controls and SCI patients showed significant BOLD signals in the core circuitry of the mirror system as the PMv and parietal cortex and the cerebellum. Activation in these regions has been described in previous fMRI studies using similar foot movements as the task of interest (Wheathon et al., 2004; Sakreida et al., 2005), although Buccino et al. (2001) did report parietal activation solely for the object-

related tasks. The control group revealed in general larger clusters in the right hemisphere as reported previously for foot movement observation by Wheathon et al., (2004). In contrast, the patient population revealed an emphasis of activation on the left side. Lateralization of activation has been shown before in a hand observation task (Decetey, 1997). The author suggested that meaningless human hand motions engage predominantly the right hemisphere while meaningful stimuli engage left hemisphere activity, a hemisphere more likely responsible for motor control (Rusthworth et al. 2003). It is tempting to transfer these findings from hand tasks to the present foot experiment. One can therefore hypothesize that the observation of this easy over-learned task in the control group has a different meaning for the subjects than the attempted performance in SCI patients. In other words, when the task is not automatically performed, as it might be in the SCI patients, the left hemisphere is stronger involved in task performance and vice versa. Regardless of this assumption there are several reasons to treat these results with caution. To begin with, the single subject analysis in the patient group showed in several cortical region spatially not overlapping clusters. It therefore remains unclear how representative the group averaged data in this experiment can be. Secondly, a recent meta-analysis for laterality effects in the mirror neuron system (Molnar-Szakas et al. 2005) and a fMRI study investigating laterality effects came to the conclusion that motor resonance behavior is bilaterally distributed (Aziz-Zadeh et al., 2002, Aziz-Zadeh et al., 2006). The authors therefore suggested that due to differences in task conditions, caution must be applied to interpret results where laterality is of theoretical importance.

3.3.5.2. Plasticity in the execution/observation matching system

The observed and attempted task performance revealed adaptive plasticity for both tasks in the core regions of the observation/execution system in the SCI patients when compared to the control group. The results might be best understood by the entanglement of executive and visual aspects within the mirror system. A single mirror neuron in the monkey brain fire both when the animal performs or observes a similar movement, possessing therefore both visual and motor properties (Rizzolatti et al.2002). The complete sensory deprivation in the motor system might have been leading to an altered output pattern within the motor network during attempted performance. The habitual perception of other peoples moving legs could activate networks mediating a visuomotor limb representation (Wolpert et al., 1998). Grèzes

et al. (1999) suggested that the joint activation of premotor and parietal areas, as seen in the mirror system, could account for the processing of movement patterns into motor plans within the working memory and its transfer to regions capable of executing them.

3.3.5.3. Mirror system and rehabilition

Movement observation is a new type of passive paradigm to induce a motor response and can be used as an advanced tool to assess disturbances of motor disorders by means of neuroimaging methods. This method could be utilized when overt movements are not feasible in order to verify an internal generation of a motor representation and select the therapy accordingly.

Recent investigations have shown, that motor learning can occur in the absence of overt movement by simple observing the actions of others, in spite of the lack of proprioceptive input: The human motor system seems to be able to incorporate the experiences of others in building the motor repertoire of the individual (Frey and Gerry, 2006; Mattar and Gribble, 2005). By using promoted observation of daily activities as an additional mean of therapy, Buccino and colleagues (2006) reported preliminary results about improved motor skills for the hand in hemiplegic patients.

4. CONCLUDING REMARKS

This thesis focus on mechanisms of action representation for executed, imagined and observed foot movement in healthy and SCI subjects. The patient group suffering from complete deefferentation and deafferentation due to spinal cord lesion was approached to assess the input of a distant spinal cord lesion with consecutive functional impairment on the reorganization of motor control. By using fMRI, a method to study activity dependent anatomo-functional correlations, several findings could be gained: 1) Activation networks in SCI patients for executed, imagined and observed foot movements are similar to the ones in healthy controls. 2) In chronic complete SCI patients the brain remains able to control motor behavior at various levels due to an internal movement representation. This internal movement representation has been confirmed by the activation of the observation/execution matching system. 3) The patient group showed plastic changes related to the spinal lesion. These investigations in SCI patients allowed conclusions on behavior-brain interactions and motor control without proprioception. Results are discussed in the frame of future rehabilitation strategies.

4.1. Shared motor representations for execution, imagination and observation

The three studies of this thesis establish the physical embodiment for overt and covert foot movements in healthy controls and its organization after a complete lesion of the spinal cord. The cognitive processes of interest (internal simulation and observation) are supposed to be closely related to the generation and execution of potential actions and therefore require the involvement of a motor representation.

The data presented in this thesis and in previous neuroimaging studies have shown an overlap between action execution, simulation, and observation in the ventral premotor and parietal cortices, and in basal ganglia and cerebellum. However, both mental simulation and observation of actions, engage slightly different portions of these brain regions. This suggests different degrees of activation in these tasks. The activation patterns further show complex distributed circuits that share several cortical regions, all fundamentally involved in various levels of motor performance. More important, all conditions share a common mechanism: the simulation of actions by means of the activation of premotor, parietal, and subcortical networks. This finding is in accordance with the theory that movement

representation is stored within these brain regions, an idea that is supported by studies with apraxic patients (Buxbaum *et al*., 2003; Fukutake, 2003) and by neuronal correlates in monkeys (Rizzolatti and Craighero, 2004; Rizzolatti *et al*., 1996a).

4.2. Differentiation between executed and imagined movements without proprioceptive feedback

Motor imagery is an active mental rehearsal during which subjects internally simulate a motor act stored within their working memory without visible body movements. The question remains how SCI patients were capable of differentiating attempted and imagined movements without somatosensory feedback, as kinesthetic imagery (i.e. the feeling of one's own limb moving) instead of visualization of the movement was required. Undoubtedly, the fMRI data revealed different activation patterns for task, movement attempt or motor imagery, and the previously assessed behavioral data showed comparable findings. A possible explanation might come from a case report by Schwoebel and colleagues (2002). They investigated a patient (CW) with bilateral parietal lesion after two strokes that executed "imagined" hand movements. CW was not aware that he was moving his hand although the imagined movements were more accurate than the executed ones. CW's uninhibited movements during motor imagery suggest that the parietal areas may normally play a critical role in inhibitory processes. This role has been attributed to the inferior frontal cortex (Deiber *et al*., 1998). The findings suggest a functional and anatomical dissociation in parietal regions between cortical areas underlying movement simulation and execution. This more specialized network for motor imagery has been reported in several studies comparing it with execution (Lotze et a., 1999; Gerardin *et al*., 2000; Hanakawa *et al*., 2003).

4.3. Functional adaptation in SCI patients

A common finding in all studies directly comparing SCI patients and healthy controls data was the stronger activation in premotor and parietal cortex and, subcortically, in basal ganglia and cerebellum. The changes were mere enlargements of activation and did not reveal any topographic reorganization. In the following sections possible hypothesis are formulated to explain these plastic changes in SCI patients.

4.3.1. Vision of a limb provides information about properties of the limb

Execution of a motor act requires knowledge of the location of body parts in space. Recent models of motor control propose that this information is provided by two major sources. First, the "forward model" assumes that an efference copy will predict the location of a body part in action. The second source of information regarding body part position is provided by feedback from sensory systems (Wolpert and Ghahrami, 2000). There are at least two main sensory inputs providing an on-line feedback, namely vision and proprioception. The exact contribution of these two sensory inputs remains unclear. The integration of the processes (i.e. efference copy and sensory feedback) has been hypothesized to produce an on-line, real-time representation of the body position that has also been termed "body schema" (Schwoebel and Coslett, 2005). In complete SCI patients there is no recovery of proprioceptive sense but a possible compensation by cognitive control, i.e. attention and vision might have been successful in rebuilding or maintaining the body schema. There are a handful of patients without proprioceptive inflow, who provide a human model in which the effects of deafferentation with still intact motor output can be studied. Gallagher and Cole (1995) described a subject who was suffering from acute pure sensory neuropathy, resulting in the lack of both proprioceptive function and sensation of touch below the neck. Despite the loss of proprioception, the patient recovered movement control, relying heavily on attentive visual cues. In line with this single case report, the accuracy of reaching movements in patient's suffering from the same fate was investigated by Ghez and colleagues (1995). These patients showed improved task performance by looking at their hands during movements or by vision of the limb on preceding trials. The authors suggested that vision of the limb provided the participants with information about their limb properties that they could use to program a range of movements and therefore to form or/and update an internal representation of the limb. However, these patients cannot constantly update their internal body representation; therefore the question arose of how long this effect may persist. The data indicate that performance is considerably degraded within a few minutes once vision of the limb is no longer available. It may appear surprising that the effects of vision of the limb, and therefore the representation of the limb's properties in memory, should be so transitory in patients. This suggests that internal models of the dynamic properties of the limb used for planning reaching movements require continuous updating (Ghez *et al.*, 1995).

4.3.2 Internal representation of one's body

It can be assumed that the parietal areas and the cerebellum work as functional loops estimating the current status of the motor system throughout motor performance. The enhanced activation in these key regions, detected in all three studies in the SCI patients when compared to data in the controls, strongly indicates an adaptation of the body schema to the novel condition. In fact, individuals with complete paraplegia, who are confined to execute movements from limited anatomical positions (primarily sitting), receive input from various sensory channels (e.g., proprioceptive, vestibular, tactile, visual, efference copy) in a different way than previously to the injury. Additionally, due to the deefferentation and deafferentation condition, the brain is not only deprived from proprioceptive input but also lost the actual efferent control of the lower body part.

It is of high importance in the context of the presented investigations that complete SCI patients experience a vivid perception of their disconnected lower body. Sensory phenomena in a region with complete denervation, such as occurs after amputation, are often referred to as „phantom" sensation. Although non-painful sensory phantom phenomena have been described after spinal cord injury, there is little information available about the prevalence and duration of these sensations or about the relation with other variables associated with the injury "Spinal phantoms" often escape the attention of the clinician because they are, in the first line, not specifically inquired, but also are less vivid and usually less persistent than amputation phantoms (Spitzer *et al*., 1995), (Bors, 1951) and often confounded by the patient with residual sensations such as pain and paresthesias (Burke and Woodward, 1976). It has been suggested that the prevalence of phantom sensations after traumatic spinal cord injury is as high as 89% or 100% (Bors, 1951, Conomy, 1973; Ettlin, 1980; Siddal &McClelland, 1999). Most importantly in the context of the present thesis, phantom leg sensations can be "suppressed" or altered by visual feedback from looking at one's own paralyzed limbs (e.g., Conomy, 1973) – a feedback that it obviously not present in amputees. For the interpretation of our results in the execution and imagination tasks it was important to investigate the phantom sensations in SCI patients with a structured interview previously to the scanning session (see methods section of Study 2 and Appendix B). Own results from these interviews confirm the observations reported previously. The patients usually experience phantom body sensations immediately after injury. The phantom legs may be "frozen" in the position the legs had obtained during the accident. Looking at one's own

paralyzed legs can correct this phantom position. Within a few days this incongruence between the perceived and the visualized position is gone (see also Conomy 1973). In addition, interviews with chronic SCI patients revealed that they never experienced any telescoping of the lower extremities (i.e. shrinking of the size), a finding usually described in amputees when they were not wearing their prosthesis (unpublished results). In fact, the visual updating of the extent of ones limb in SCI patients might explain these differences with the sensory phenomena described by in amputees.

4.4. Clinical implications

All aspects of an action appear to be involved in motor imagery and movement observation. It seems thus a logical consequence of this fact is that a subsequent execution will be facilitated. This facilitation would explain various forms of training (e.g., mental training) and learning (e.g., observational learning) which occur during covert actions (Pascual-Leone *et al*., 1995). In addition, imitation would be based on directly matching the observed action onto an internal simulation of that action (Iacoboni *et al*., 1999).

4.4.1. Improving rehabilitative strategies

Results from sport psychology and skilled motor learning show that mental practice with motor imagery techniques indeed improves the subject's performance when compared to no-practice control conditions. Motor imagery would therefore be beneficiations both for rehearsing skilled movements as well as for learning a new movement, even when this effect is smaller than in physical practice (Feltz and Landers, 1983; Driskell *et al*., 1994, Jackson *et al*., 2003, Lacourse *et al*., 2005). One postulated mechanism for the benefit of imagery is the potentiation of synaptic transmission that occurs during both motor imagery and actual execution.

As in mental imagery only few studies have investigated the role of the observation /execution system for motor learning. Stefan *et al*. (2005) reported increased activation after observation of thumb movements away from the baseline movement direction. Mattar and Gribble (2005) used kinematics analyses to show that the acquisition of complex motor behavior (learning to reach in a novel mechanical environment) is facilitated by previous

observation of subjects learning the novel task. Motor learning by observation was impaired when the motor system was engaged with an unrelated movement task. Both findings provide evidence for the notion that observation alone may induce lasting specific changes in motor representation, a kind of motor memory, similar to that induced by practicing movements, even in absence of peripheral somatosensory afferent information.

A great-unused potential lies in these training methods as a therapeutic tool. The results mentioned above add to the arguments in favor of the use of motor imagery and movement observation in neurological rehabilitation. First, action observation recruits the motor system as doe's motor execution. Second, during the imitation of a novel motor pattern, the mirror neuron system is active from the observation phase until the execution of the new action. Buccino et al. (2006) described a possible therapy approach in an ongoing, multicenter trial where action observation and imitation are being used systematically as mental practice aimed at improving motor performance in patients with ischemic stroke.

This therapy does not replace, but augments, conventional neurorehabilitation on the basis of passive or active execution of movements. During the treatment, patients are asked to carefully observe short movies, each lasting about 15 minutes. In each of these video-sequences a different daily action (i.e., having a coffee, eating an apple) is presented. In the entirety of the study, 20 daily actions are practiced. In the visual stimuli, actions are segmented into their principal motor acts: for example the action ''having a coffee'' consists of the following components: grasping the cup, putting sugar in it, stirring, bringing to the mouth. During the training session, the patient is assisted by a physiotherapist who helps the subject maintain attention and motivation. After each single act, patients are required to execute the observed action with their impaired upper limb. Before, during, and after the treatment patients undergo a functional evaluation by means of functional scales to evaluate the impairment of the upper limb in everyday activities.

The results showed that patients undergoing the treatment experienced subjective improvement. Further they showed better motor performance as revealed by functional scales (Barthel Index, Functionally Independence Measure, Frenchay Arm Test, Fugl-Meyer).

These lines of evidence described above raise the possibility of improving motor performance through systematic exercise based on careful observation and imitation of everyday actions. It may be especially useful to aid in recovery in patients who have

difficulties in generating physical movements (i.e. incomplete spinal cord injury, Guillain Barré or brain injury) or who are unable to understand verbal instructions.

4.4.2. Converting thoughts into action

The retained motor representations in the SCI patients seem to be one of the principal physiological requirements for the development of a brain-computer interface device. Although it may someday be possible to reconnect damaged neural pathways by directing the regrow of neurons, neuroprosthetics provide another potential approach to permit individuals with severe neurological injuries to interact with the environment.

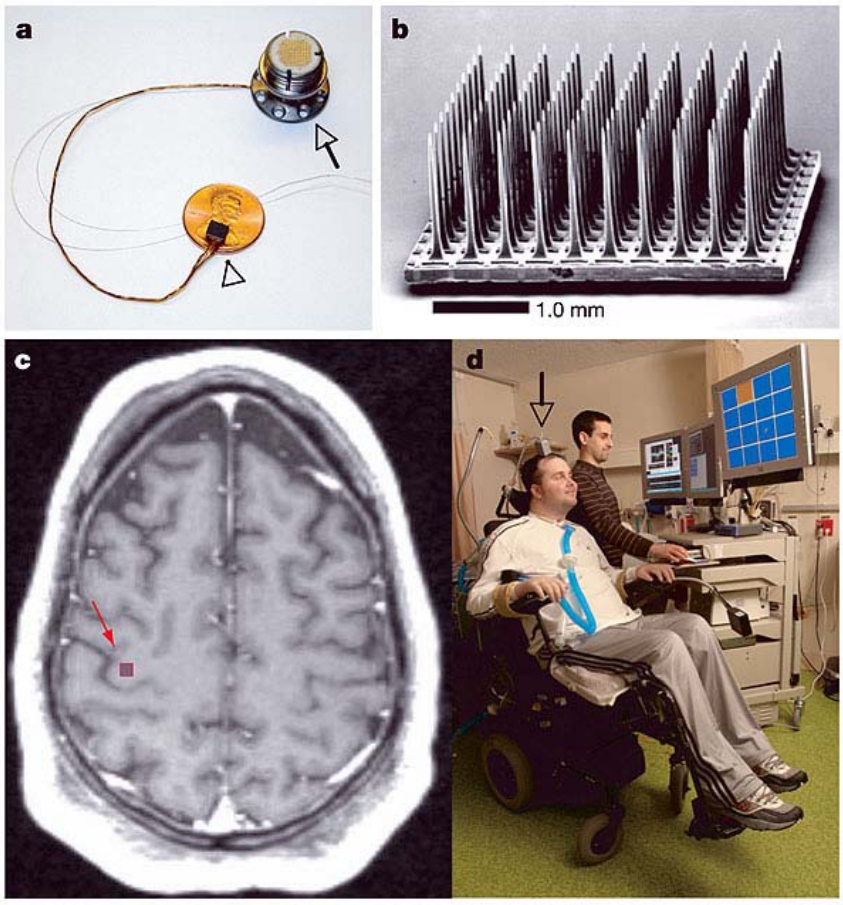


Figure 1. a, The BrainGate sensor (arrowhead), resting on a US penny, connected by a 13-cm ribbon cable to the percutaneous Ti pedestal (arrow), which is secured to the skull. Neural signals are recorded while the pedestal is connected to the remainder of the BrainGate system (seen in **d**). **b**, Scanning electron micrograph of the 100-electrode sensor, 96 of which are available for neural recording. Individual electrodes are 1-mm long and spaced 400 μm apart, in a 10 ×10 grid. **c**, Pre-operative axial T1-weighted MRI of the brain of participant 1. The arm/hand 'knob' of the right precentral gyrus (red arrow) corresponds to the approximate location of the sensor implant site. A scaled projection of the 4 ×4-mm array onto the precentral knob is outlined in red.

d, The first participant in the BrainGate trial (MN). He is sitting in a wheelchair, mechanically ventilated through a tracheostomy. The grey box (arrow) connected to the percutaneous pedestal contains amplifier and signal conditioning hardware; cabling brings the amplified neural signals to computers sitting beside the participant. He is looking at the monitor, directing the neural cursor towards the orange square in this 16-target 'grid' task. A technician appears (A.H.C.) behind the participant (Hochberg *et al*., 2006).

Several different approaches have been developed ranging from non-invasive technologies such as electroencephalography (EEG) activity using removable electrodes placed on the scalp surface, to implantable devices that use microelectrodes to detect the activities of individual neurons (Scott, 2006). Neuromotor prostheses (NMPs) aim to replace or restore lost motor functions in paralyzed humans by routing movement-related signals from the brain, around damaged parts of the nervous system, to external effectors. To translate preclinical results from intact animals to a clinically useful NMP, movement signals must persist in cortex after spinal cord injury and be engaged by movement intent when sensory inputs and motor control of the limb are lacking. Furthermore, NMPs would require that intention-driven neuronal activity be converted into a control signal that enables useful tasks. Hochberg *et al*., (2006) recently reported initial results for a tetraplegic human using a pilot NMP (Picture X).

Neuronal ensemble activity recorded through a 96-microelectrode array implanted in primary motor cortex demonstrated that intended hand motion modulates cortical spiking patterns three years after spinal cord injury. Decoders were created, providing a ‘neural cursor’ with which the patient opened e-mails and operated devices such as a television, even while conversing. Furthermore, the patient used neural control to open and close a prosthetic hand, and perform rudimentary actions with a multi-jointed robotic arm. These early results suggest that NMPs based upon intracortical neuronal ensemble spiking activity could provide a valuable new neuron-technology to restore independence for humans with paralysis.

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7. CURRICULUM VITAE

Sabina Hotz Boendermaker

Personal Details

Date of Birth	26th May 1967
Marital Status	Married, 2 children: Anna Sofie 2004; Lynn Elise 2006
Nationality	Swiss

Academic Education

2002 – 2006	PhD student in Psychology at the Spinal Cord Injury Center, Balgrist University Hospital and University of Zurich, Department of Neuropsychology, Switzerland
2002 – 2006	International Ph.D. Program in Neuroscience, Neuroscience Center Zurich, University and ETH Zurich, Switzerland
1995 – 2001	Student in Psychology at University of Zurich, Switzerland, main topics Applied Psychology, Neurophysiology and Neuropsychology, MS Degree in Psychology, Licenciata philosophiae
2000	Practical training in Neuropsychology, Department of Neuropsychology, University Hospital Zurich, Switzerland
1988 – 1992	Student in Physiotherapy, School for Physiotherapy, University Hospital Zurich, Switzerland, Diploma in Physiotherapy

Employments

2002 - 2006	PhD student position at the Spinal Cord Injury Center, Balgrist University Hospital
1995-2001	Freelance physiotherapist in own practice
1994-1995	Physiotherapist in regional Hospital of Maennedorf, Switzerland
1992-1994	Physiotherapist in University Hospital Zurich, Switzerland

Academic Employments

2000	Course Assistant at the Department of Neurophysiology, University of Zurich
1994-1995	Clinical instructor, School for Physical Therapy, University Hospital Zurich, Switzerland

Publication List

Alkadhi, H, Crelier, GR, Boendermaker SH, Hepp-Reymond MC & Kollias SS. (2002). Somatotopy in the ipsilateral primary motor cortex. Neuroreport 13, 2065-70.

Curt, A, Alkadhi, H, Crelier, GR, Boendermaker SH, Hepp-Reymond MC & Kollias SS. (2002). Changes of non-affected upper limb cortical representation in paraplegic patients as assessed by fMRI. Brain, 125, 2567-78.

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Alkadhi, H, Brugger, P, Boendermaker SH, Crelier, GR, Curt A, Hepp-Reymond MC & Kollias SS. (2005).What disconnection tells about motor imagery. Evidence from paraplegic patients. Cerebral Cortex, 15, 131-40.

Submitted papers

Funk, M., Lutz, K., Hotz Boendermaker, S., Roos, M., Summers, P., Brugger, P., Hepp-Reymond, M.C., & Kollias, SS. Alteration of the sensorimotor tongue representation in subjects with unilateral upper limb amelia. Neuroimage, (submitted)

Hotz Boendermaker, S, Funk, M, Summers, P, Brugger, P, Hepp-Reymond, MC, Kollias, SS & Curt, A. Preservation of motor programs in paraplegics as demonstrated by attempted and imagined foot movements. Neuroimage, (submitted)

Other congress contributions

Funk, M., Hotz Boendermaker, S., Boeni, T., & Brugger, P. (2003). Use of a functional prosthesis alters painful and non-painful phantom sensations in leg amputees. Poster presented at the Symposium of the Neuroscience Center Zurich, Zurich.

Hotz Boendermaker, S., Funk, M., Summers, P., Hepp-Reymond, M.-C., Burrack, A., Brugger, P., & Kollias, S.S. (2003). Influence of objects on brain activation during action observation, Poster presented at the Symposium of the Neuroscience Center Zurich, Zurich.

Funk, M., Hotz Boendermaker, S., Lutz, K., Summers, P., Brugger, P., Hepp-Reymond, M.-C., & Kollias, S.S. (2004). Neural substrates of first- and third person motor imagery, Poster presented at the 34th Annual Meeting of the Society of Neuroscience, San Diego.

Funk, M., Lutz, K., Hotz Boendermaker, S., Summers, P., Brugger, P., Hepp-Reymond, M.-C, & Kollias, S.S. (2004). Cortical tongue representation in dysmelic patients, Poster presented at the Symposium of the Neuroscience Center Zurich, Zurich.

Dokladal, P., Hotz Boendermaker, S., Brugger, & A. Curt (2004). Are non-painful phantom sensations influenced by internal or external factors? Poster presented at the Symposium of the Neuroscience Center Zurich, Zurich.

Hotz Boendermaker, S., Funk, M., Summers, P., Brugger, P., Hepp-Reymond, M.-C, & Kollias, S.S. (2005). Are there differences in the observation/execution matching networks for hand and foot tasks?, Poster presented at the annual meeting of the Swiss Society for Neuroscience.

Hotz Boendermaker, S., Funk, M., Summers, P., Brugger, P., Hepp-Reymond, M.-C, Curt, A. & Kollias, S.S. (2005). Similar functional reorganization during execution, imagery and observation of hand movements in paraplegic patients, Poster presented at the Symposium of the Neuroscience Center Zurich, Zurich.

Hotz Boendermaker, S., Funk, M., Summers, P., Brugger, P., Hepp-Reymond, M.-C, Curt, A. & Kollias, S.S. (2006). Different activation patterns between attempt to move and motor imagery in paraplegic patients, Poster presented at the Gait and mental imagery congress in Madrid